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Strictly Regiocontrolled α-Monosubstitution of Cyclic Carbonyl Compounds with Alkynyl and Alkyl Groups via Pd-Catalyzed Coupling of Cyclic α-Iodoenones with Organozincs[1]

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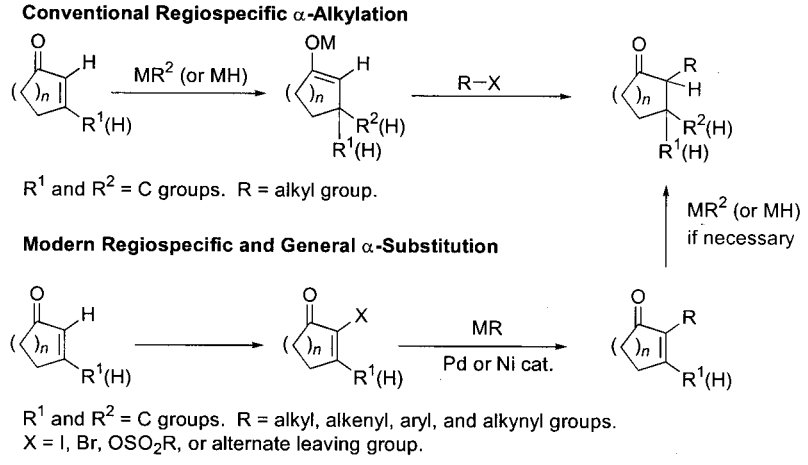
Abstract—The conditions for the Pd-catalyzed cross coupling of cyclic α-iodoenones, such as 2-iodo-2-cyclohexenone, with alkynylzincs have been optimized. The use of tris(*o*-furyl)phosphine (TFP) as a ligand and DMF as a solvent has led to the formation of α-alkynylenones in excellent yields. This optimized procedure has been applied to the synthesis of (±)-harveynone and (±)-tricholomenyn A in high yields. Investigation of related α-alkylation reactions using alkylzincs has revealed the following. Methylzinc and primary alkylzinc derivatives readily undergo Pd-catalyzed cross coupling with α-iodoenones. Although $(s\text{-Bu})_2Zn$ also undergoes Pd-catalyzed cross coupling, only the *n*-Bu-substituted products were obtained. α-Benzylation and α-homobenzylation can proceed satisfactorily, whereas allylzinc and propargylzinc derivatives undergo only addition to the carbonyl group. Although some promising results have been obtained in α-homoallylation and α-homopropargylation, these reactions need to be further improved.

Introduction and Background

α-Substitution of carbonyl compounds with a carbon group, as exemplified by enolate alkylation,[2] is a fundamentally important organic transformation. While there are many favorable cases of enolate alkylation, it has also been plagued with some serious limitations and difficulties. Thus, the scope of α-substitution of alkali and alkaline earth metal enolates under the usual thermal conditions is essentially limited to introduction of certain types of alkyl groups, such as Me, primary alkyl, allyl, and benzyl. Although its scope was expanded so as to include α-arylation through the development of radical processes ($S_{RN}1$),[3] its application to α-alkenylation and α-alkynylation remains largely unexplored. Earlier efforts to promote α-arylation and α-alkenylation of enolates with transition metals, such as Ni and Pd,[4] led to some promising results, but the results were often disappointing. Recent reinvestigations along this



Scheme 1.

Keywords: α-iodoenones; tris(*o*-furyl)phosphine; Pd-catalyzed cross coupling.

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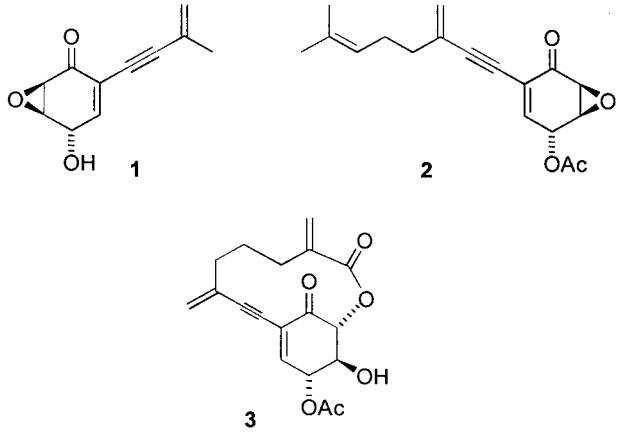
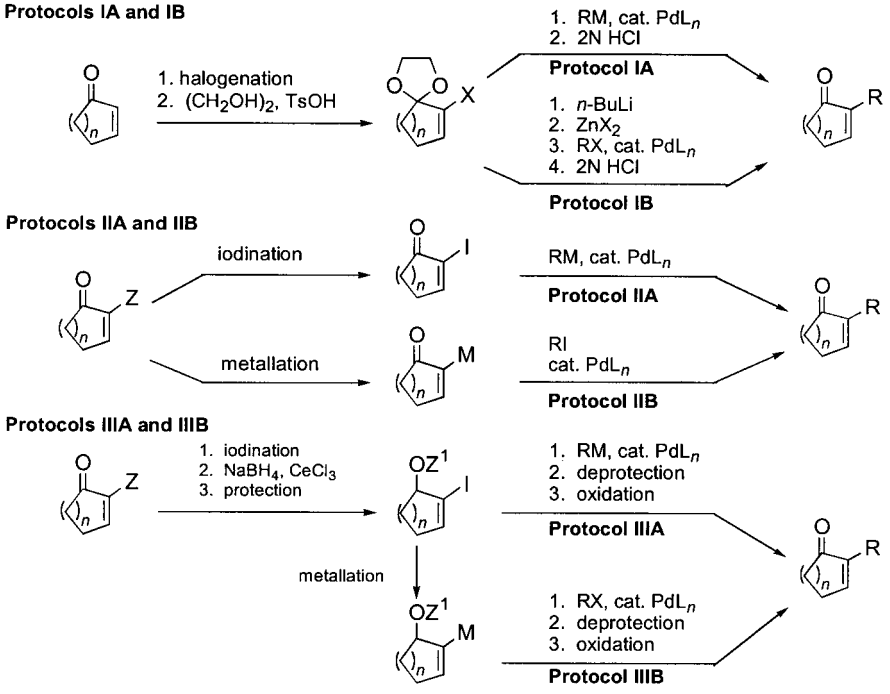
line[5] have led to more favorable results. However, their attention has been largely focused on α-arylation. Furthermore, strict control of regiochemistry of α-substitution remains largely unattended. Among other methods for α-substitution, α-alkenylation and α-alkynylation of β-keto ester with alkenyl- and alkynyl leads[6] are noteworthy. In view of their somewhat circuitous nature and the use of $Pb(OAc)_4$ as a stoichiometric reagent, however, the development of alternate and potentially more favorable procedures would be desirable. Some other indirect methods for α-alkenylation of carbonyl compounds[7] should also be noted.

In light of the well-known two-step regiospecific protocol involving (i) conjugate reduction or addition of α,β-unsaturated enones to regiospecifically generate enolates and (ii) regiospecific α-substitution,[8] we envisioned a novel strictly regio-controlled and potentially general alternative for α-substitution of carbonyl compounds outlined in Scheme 1. In this study, our attention has been focused on α-substitution of cyclic enones with alkynyl and alkyl groups that are potentially applicable to the synthesis of complex natural products and related compounds. In 1987, we reported the first generation protocol (Protocol I)[9] involving (i) conversion of enones to carbonyl protected α-iodoenone derivatives,[10] (ii) Pd- or Ni-catalyzed organozinc cross coupling,[11] and (iii) conjugate reduction[12] or addition[13] (Scheme 2). In 1991, we introduced the second generation protocol (Protocol II)[14] involving direct Pd-catalyzed cross coupling of α-iodoenones (Scheme 2). The synthetic utility of this protocol was further elevated by subsequent developments of modified procedures for the synthesis of α-iodoenones,[15] and various analogues of the second generation protocol have since been developed.[16] Until several years ago, however, the scope of the second generation protocol was essentially limited to α-alkenylation and α-arylation.[14,16a,17]

Recent discoveries of natural products containing α-alkynylenones, such as harveynone (**1**)[18] and tricholomenyns A (**2**) and B (**3**),[19] prompted us to further extend the scope of the Protocol II so as to accommodate α-alkynyl groups. In the meantime, a few isolated examples of alkylation[16c,16d] and alkynylation[1,16f] as well as a systematic application of the Sonogashira coupling[20] to α-alkynylation and its application to the synthesis of harveynone(**1**) and tricholomenyn A (**2**)[1,16f] have been reported over the past several years. Although more cumbersome and plagued with a few competitive side reactions, an earlier report on Pd-catalyzed alkynylation of β-bromoallylic acetates[21] is also noteworthy.



The feasibility of developing the Pd-catalyzed α-substitution of α-metalloenones, i.e., Protocol IIB, was examined, for the first time, with α-(trimethylstannyl)-2-cyclopentenone



Scheme 2. n=1 or 2. M=Zn, Sn, Cu, B, and other metals. R=C groups. Z=H, Si or Sn group. X=I, Br or Cl. Z^1=Si or another protecting group.

Table 1. Pd-catalyzed reaction of 2-iodo-2-cyclohexenone with alkynylzincs (the reaction was carried out at 23°C)

RC≡CZnX[a]	Initial countercation[b]	Catalyst[c]	Solvents	Time (h)	Product yield by ^{1}H NMR (%)
(*n*-BuC≡C)$_2$Zn	Li	A	Hexane–THF–DMF	12	15
n-BuC≡CZnBr	Li	A	Hexane–THF–DMF	12	28
n-BuC≡CZnBr	Li	B	Hexane–THF–DMF	2	45
n-BuC≡CZnBr	Li	B	DMF[d]	1	90
n-BuC≡CZnBr	MgBr	B	DMF[d]	1	80
(*n*-BuC≡C)$_2$Zn	Li	B	DMF[d]	1	60
H$_2$C=C(Me)C≡CZnBr	Li	B	DMF[d]	0.5	87[e]

[a] The amount of the starting alkyne relative to 2-iodo-2-cyclohexenone was 1.3 in all cases.
[b] Either *n*-BuLi or EtMgBr was used for metallation of the terminal alkyne.
[c] A=Cl$_2$Pd(PPh$_3$)$_2$; B=Pd(dba)$_2$/TFP.
[d] The other solvents, i.e. hexane and THF, were evaporated before addition of DMF.
[e] Isolated yield.

prepared from α-bromo-2-cyclopentenone via protection–lithiation–stannylation–deprotection.[14] As desired, its Pd-catalyzed coupling with (*E*)-1-iodo-1-octene proceeded in 80% yield, but the same alkenylation of 2-(trimethylstannyl)bicyclo[3.3.0]oct-1-en-3-one failed.[14] And yet, the use of cyclic enone derivatives as nucleophiles is critically desirable in cases where the α-side chain cannot be a part of an organometallic reagent and must therefore be a component of an electrophile. This and other requirements, such as avoiding acidic reaction and workup conditions, prompted us to develop yet another alternative, i.e. Protocol III in Scheme 2, as a highly reliable and general, if somewhat more indirect, method of α-substitution of carbonyl compounds.[21,22] This protocol has been applied to the synthesis of nakienones A[22a] and B[22b] as well as carbacyclin,[22c] in which Protocols I and II were unsatisfactory. It has also been used by other workers[23] in a recent synthesis of (−)-tricholomenyn A to circumvent difficulties in the direct use of the α-iodocyclohexanone derivative for coupling with the alkynyl sidechain. A review discussing various aspects of α-substitution of carbonyl compounds including the topics of this paper has recently been published.[24]

In this study, our attention is focused on the Pd-catalyzed α-alkynylation and α-alkylation of 2-iodocycloalkenones with alkynyl- and alkylmetals containing Zn (Protocl IIA), which are to supplement our earlier studies of the Pd-catalyzed α-arylation and α-alkenylation.[9,14]

Results and Discussion

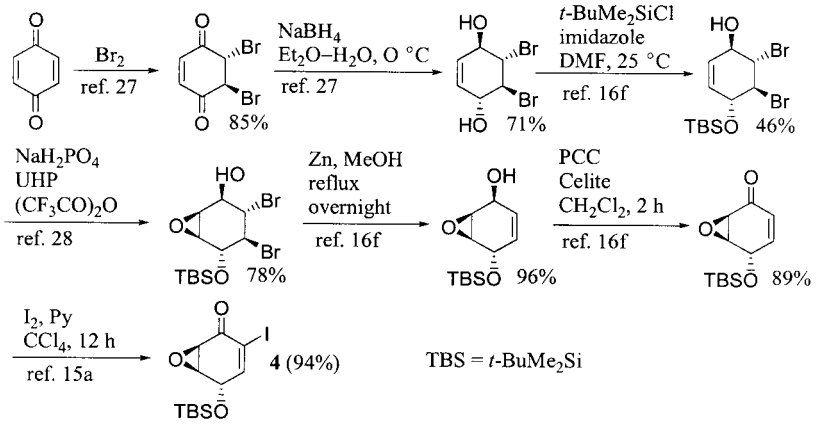
Pd-Catalyzed α-alkynylation of α-iodoenones with alkynylzincs and its application to the synthesis of (±)-harveynone and (±)-tricholomemyn A

Our earlier success in the development of various procedures of Pd-catalyzed α-arylation and α-alkenylation[9,14,22] prompted us to develop related α-alkynylation procedures. Our interest was further aroused by the isolation and identification of naturally occurring α-alkynylenones, such as (+)-harveynone (**1**)[18] and (−)-tricholomemyn A (**2**),[19] and a reported difficulty[23] in achieving α-alkynylation of α-iodoenones by the Sonogashira reaction.[20] We therefore decided to develop an alternative procedure for α-alkynylation based on our previously developed Pd-catalyzed cross coupling of alkynylzincs.[25]

The reaction of 2-iodo-2-cyclohexen-1-one with 1-hexynylzinc bromide, generated in situ by treating 1.3 equiv. of 1-hexyne with *n*-BuLi (1.3 equiv.) and 1.3 equiv. of dry ZnBr$_2$ in hexane–THF, was carried out in the presence of 5 mol% of Cl$_2$Pd(PPh$_3$)$_2$ and DMF added as a cosolvent. Although the starting 2-iodo-2-cyclohexenone was consumed in 12 h at 25°C, the desired 2-(1-hexynyl)-2-cyclohexenone was formed only in 28% yield (^{1}H NMR). The yield observed with 0.65 equiv. of bis(1-hexynyl)zinc was 15%. Since we earlier noted that tris(2-furyl)phosphine (TFP)[26] was superior to PPh$_3$ in the Pd-catalyzed α-alkenylation of α-iodocyclenones[14] and related iodoallylic alcohol derivatives,[22] we replaced Cl$_2$Pd(PPh$_3$)$_2$ with 5 mol% of Pd(dba)$_2$ and 10 mol% of TFP and observed the formation of 2-(1-hexynyl)-2-cyclohexenone in 45% (^{1}H NMR). When the solvents used for generation of 1-hexynylzinc bromide, i.e. hexane and THF, were evaporated prior to addition of DMF, the reaction run under otherwise the same conditions provided the desired product in 90% yield (^{1}H NMR). The corresponding reaction of 3-methyl-3-buten-1-ynylzinc bromide with 2-iodo-2-cyclohexenone provided the desired cross coupling product in 87% isolated yield (quantitative yield by ^{1}H NMR). These results are summarized in Table 1.

Having optimized the reaction conditions for α-alkynylation of 2-iodo-2-cyclohexenone, we turned our attention to its application to the synthesis of harveynone and tricholomenyn A. We soon learned of a related study[16f] of the synthesis of these two compounds using the Sonogashira coupling,[20] which was achieved in 52 and 54% yields, respectively. Largely following the reported procedures, (±)-4-(*t*-butyldimethylsilyl)-5,6-epoxy-2-iodo-2-cyclohexenone (**4**) was prepared in seven steps from benzoquinone in 17% overall yield, as summarized in Scheme 3.[15a,16f,27,28]

The reaction of the α-iodoenone intermediate **4** with 3-methyl-3-buten-1-ynylzinc bromide (1.3 equiv.) and 3-methylene-7-methyl-6-octen-1-ynylzinc bromide in the presence of 5 mol% of Pd(dba)$_2$ and 10 mol% of TFP in DMF at 25°C provided in 1 h TBS-protected harveynone (**5**) and a tricholomenyn A precursor (**6**) in 73 and 80% isolated yields, respectively. As such, these cross coupling yields are roughly 20–25% higher than those realized under the Sonogashira conditions.[16f] Removal of the TBS group of **5** with 48% aqueous HF in CH$_3$CN[23] provided (±)-harveynone (**1**) in 80% isolated yield. Similarly, **6** was treated with



Scheme 3. Note: The chiral compounds are racemic mixtures.

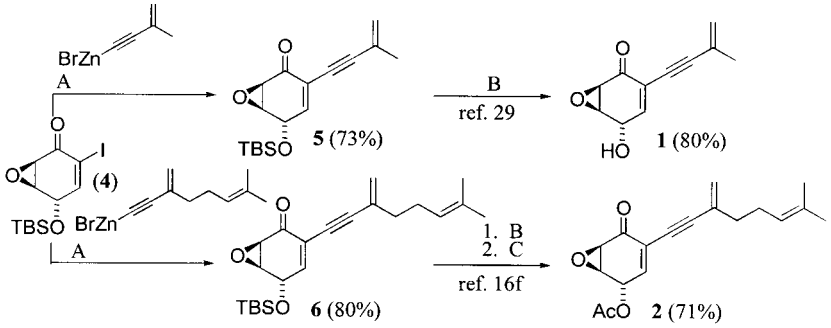
48% aqueous HF in CH_3CN[29] to provide the corresponding free alcohol in 88% isolated yield. Its treatment with HOAc (2.5 equiv.) and dicyclohexylcarbodiimide (DCC, 1.5 equiv.) in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) afforded (±)-tricholomenyn A (**2**) in 81% isolated yield. These results are summarized in Scheme 4.

In summary, the Pd-catalyzed cross coupling of alkynylzincs[25] offers a satisfactory procedure for the synthesis of α-alkynylenones. Although no rigorous comparison has been made, the available data suggest that the alkynylzinc-based procedure favorably compares with that based on the Sonogashira protocol. Although different from the reaction discussed here, another recent application of the Pd-catalyzed cross coupling with alkynylzincs[25] to α-alkynylation of α-bromo-α,β-unsaturated esters[30] also points to the superior reactivity of alkynylzincs in the Pd-catalyzed cross coupling.

Pd-catalyzed α-alkylation of α-iodoenones with alkylzincs

α-Alkylation of metal enolates and enamines proceeds satisfactorily in many cases.[2] However, it has also been associated with difficulties, such as multiple alkylation, β-elimination, and frequent lack of strict regiochemical control. In view of the favorable results observed in α-arylation, α-alkenylation, and α-alkynylation discussed above, we decided to develop a strictly regio-controlled α-monoalkylation procedure based on Pd-catalyzed cross coupling of alkylzincs[31] with α-iodoenones. In this connection, a recent study of the Pd-catalyzed reaction of *B*-alkyl-9-BBNs with α-iodoenones and its elegant application to the synthesis of prostaglandin E_1 are noteworthy.[16c]

A systematic investigation of the Pd-catalyzed reaction of various types of alkylzincs with several representative α-iodocyclopentenones and α-iodocyclohexenones was performed. The results summarized in Table 2 indicate the following. First, methyl- and primary alkylzincs including an isobutyl derivative, i.e., $(i\text{-Bu})_2Zn$, react readily with various α-iodoenones in the presence of 5 mol% of $Cl_2Pd(PPh_3)_2$. Curiously, the use of one half equivalent of $ZnBr_2$ relative to alkyllithium or alkylmagnesium halide has led to noticeably higher product yields. Secondly, the reaction of $(s\text{-Bu})_2Zn$ with 2-iodo-2-cyclopentenone under the same conditions also gives the cross coupling product in 72% NMR yield (61% isolated). However, the product is 2-(*n*-butyl)-2-cyclopentenone. Further investigation of the reaction is highly desirable. Thirdly, $(PhCH_2)_2Zn$ generated in situ by treating $PhCH_2MgBr$ with $ZnBr_2$ is rather sluggish in the Pd-catalyzed cross coupling with 2-iodo-2-cyclopentenone. On the other hand, $PhCH_2ZnBr$ generated by treating $PhCH_2Br$ with Zn smoothly gave α-benzylenones in high yields. Since addition of 1 equiv. of $MgBr_2$ to $PhCH_2ZnBr$ almost totally blocks the desired cross coupling, $MgBr_2$ must exert an inhibitory action in this particular reaction. However, the mode of inhibition with

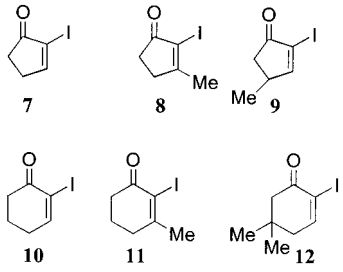


Scheme 4. A=5% $Pd(dba)_2$, 10% TFP, DMF, 23°C, 1 h. B=48% HF–CH_3CN. C=HOAc (2.5 equiv.), DCC (1.5 equiv.), cat. DMAP, 0.5 h. Note: The chiral compounds are racemic mixtures.

Table 2. Pd-catalyzed reaction of α-iodoenones with alkylzinc derivatives in the presence of $Cl_2Pd(PPh_3)_2$. (Unless otherwise mentioned, the reactions were carried out at 23°C in DMF or DMF–THF using either 0.65 molar equiv. of a dialkylzinc or 1.3 molar equiv. of an alkylzinc halide)

Entry	Alkylzinc derivative	Method of generation[a]	α-Iodoenone[b]	Product yield (%)[c]
1	Et_2Zn	A	**7**	85 (69)
2	$(n\text{-Bu})_2Zn$	B	**7**	72
3	*n*-BuZnBr	B	**7**	44
4	$(n\text{-Bu})_2Zn$	C	**8**	76 (66)
5	$(n\text{-Bu})_2Zn$	C	**9**	88
6	*n*-BuZnBr	C	**9**	51
7	*n*-BuZnBr	C	**10**	75 (63)
8	$(n\text{-Hex})_2Zn$	C	**7**	85 (81)
9	$(n\text{-Hex})_2Zn$	C	**9**	96
10	$(i\text{-Bu})_2Zn$	C	**7**	85 (73)
11	$(s\text{-Bu})_2Zn$	C	**7**	72 (61)[d]
12	$(PhCH_2)_2Zn$	C	**7**	Trace
13	$PhCH_2ZnBr$	D	**7**	82 (74)
14	$PhCH_2ZnBr$	D	**10**	94
15	$PhCH_2ZnBr$	D	**11**	72
16	$PhCH_2ZnBr$	D+$MgBr_2$[e]	**11**	Trace
17	$PhCH_2ZnBr$	D	**12**	71
18	$PhCH_2CH_2ZnBr$	E	**12**	83
19	*n*-BuC≡CCH_2CH_2ZnBr	D	**12**	41
20	$Me_3SiC{\equiv}CCH_2CH_2ZnBr$[f]	D	**10**	80 (61)
21	$H_2C{=}CHCH_2CH_2ZnBr$[f]	E	**7**	36

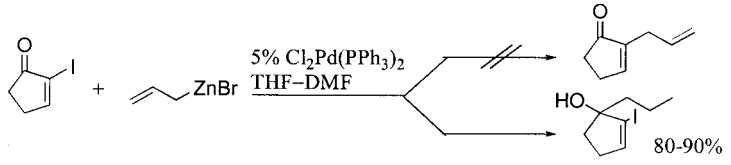
[a] A=Commericially available. B=RLi+$ZnBr_2$ (1.0 or 0.5 equiv.). C=RMgX+$ZnBr_2$ (1.0 or 0.5 equiv.). D=RX+Zn. E=RX+Mg+$ZnBr_2$.
[b] The structures of **7**–**12** are as shown below



[c] By NMR and/or GLC. The numbers in parentheses are isolated yields.
[d] Isomerized to *n*-Bu. Additionally, 3-(*s*-butyl)cyclopentanone was also isolated in 12% yield.
[e] Magnesium bromide was added to $PhCH_2ZnBr$.
[f] 5 mol% of $Cl_2Pd(TFP)_2$ or $Pd(dba)_2$+2 TFP was used as a catalyst.

$MgBr_2$ is not clear at this time. Fourthly, in sharp contrast with $PhCH_2ZnBr$, allylzinc bromide or diallylzinc undergoes an exclusive 1,2-addition to the C=O group. Little or no α-allylation has been observed (Scheme 5). Under the same conditions, propargylzinc bromide, generated in situ by treating propargyl bromide with Zn reacted with 2-iodocyclopetenone to give the 1,2-addition product in 89% yield (80% isolated). In this connection, however, a recent report on the Pd-catalyzed reaction of (2-(trimethylstannyl)-3-methyl-2-cyclopentenone with allyl bromide to give the α-allylated product in 89% yield is noteworthy.[32] Fifthly, a brief survey of homobenzylation, homoallylation, and homopropargylation indicates that $PhCH_2CH_2ZnBr$ reacts normally as a primary alkylzinc derivative to give the desired α-substitution product in high yield. On the other hand, α-substitution with homoallylzinc and homopropargylzinc derivatives is much more sluggish, which may be attributable to chelation by the homoallyl and homopropargyl groups. Favorable results observed with Me_3Si-C≡CCH_2CH_2ZnI suggest that the steric requirements around the C=C and C≡C bonds may be significant. Further investigation to clarify these intricate aspects is clearly desirable.

No difficulty was encountered in converting 2-(*n*-butyl)-2-cyclopentenone and 2-benzyl-2-cyclopentenone into their conjugate reduction products in 81 and 98% isolated yield, respectively, with Ph_2SiH_2 (2 equiv.), $ZnCl_2$, 2% $Pd(PPh_3)_4$, and 5% Me_3SiCl in $CHCl_3$.[33] Many other known conjugate reduction[12] or conjugate addition[13] procedures should be applicable to the synthesis of α-substituted cyclic ketones without the α,β-C=C bond.



Scheme 5.

In summary, the Pd-catalyzed α-substitution of 2-iodoenones with organozincs containing Me, primary alkyl, benzyl, and homobenzyl groups generally proceed in high yields. The reaction with homoallyl- and homopropargylzincs shows considerable promise but needs to be further developed. At this point, it is not clear if the difficulties associated with secondary alkylzincs and allylzincs can be overcome. α-Substitution with tertiary alkylzincs is anticipated to be more problematical than that with secondary alkylzincs.

Experimental

General procedures

All reactions were carried out under dry Ar atmosphere, unless otherwise indicated. THF was freshly distilled from sodium/benzophenone. DMF was dried over 4 Å molecular sieve. $ZnBr_2$ was flame-dried in vacuo (1 mmHg). The other commercially available reagents were used directly, unless otherwise indicated. Reactions were monitored by GLC and TLC analysis of reaction aliquots. GLC and NMR yields were determined by using hydrocarbons and dibromomethane, respectively, as internal standards. Flash chromatography was carried out on 230–400 mesh silica gel 60. GLC analysis was performed on a HP 6890 Gas Chromatograph using an HP-5 capillary column (30 m×0.32 mm, 0.5 μM film) or a column packed with SE-30 on Chromosorb W. IR spectra were recorded on Perkin–Elmer 1800 or 2000 FT-IR. ^1H and ^{13}C NMR were recorded on Varian Gemini 200 (200 MHz).

Preparation of α-iodoenones

2-Iodo-2-cyclopenten-1-one.[15a] *Representative Procedure.* In a 1-L round-bottomed flask immersed in a water bath and equipped with an addition funnel were placed 2-cyclopenten-1-one (15.0 mL, 0.18 mmol) and 1/5 pyridine–CH_2Cl_2 (300 mL). To this were added dropwise I_2 (56.8 g, 0.22 mmol) and 300 mL of 1/5 pyridine–CH_2Cl_2. The mixture was stirred for 1 h, quenched with 1N HCl, and extracted with CH_2Cl_2. The combined organic layers were washed with aqueous $Na_2S_2O_3$ and brine, dried, and concentrated. The crude product was purified by column chromatography (silica gel, 10/1 hexane–EtOAc) to afford the desired product (23.9 g, 64%): ^1H NMR ($CDCl_3$, Me_4Si) δ 2.45–2.6 (m, 2H), 2.75–2.9 (m, 2H), 8.04 (t, J=2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 30.97, 31.31, 102.87, 169.66, 204.08.

2-Iodo-3-methyl-2-cyclopenten-1-one.[15a] This compound was prepared according to the Representative Procedure from 3-methyl-2-cyclopenten-1-one (9.60 g, 0.10 mmol) in 59% yield (13.1 g): ^1H NMR ($CDCl_3$, Me_4Si) δ 2.15–2.35 (s, 3H), 2.5–2.7 (m, 2H), 2.7–2.9 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 21.92, 32.96, 34.08, 102.28, 179.87, 203.34.

2-Iodo-4-methyl-2-cyclopenten-1-one.[15a] This compound was prepared from 4-methyl-2-cyclopenten-1-one (8.00 g, 8.3 mmol) in 61% yield (11.2 g): ^1H NMR ($CDCl_3$, Me_4Si) δ 1.26 (d, J=6.2 Hz, 3H), 1.95–2.2 (m, 1H), 2.6–2.9 (m, 1H), 3.0–3.3 (m, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 19.46, 37.88, 39.13, 101.39, 174.48, 203.01.

2-Iodo-2-cyclohexenone.[15a] This compound was prepared in 53% yield (11.9 g) from 2-cyclohexenone (10.2 mL, 100 mmol) according to the Representative Procedure: mp 46–47°C; ^1H NMR ($CDCl_3$, Me_4Si) δ 2.0–2.15 (m, 2H), 2.4–2.5 (m, 2H), 2.6–2.7 (m, 2H), 7.78 (t, J=4.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 22.78, 29.98, 37.46, 103.84, 159.63, 192.23.

2-Iodo-3-methyl-2-cyclohexenone.[15a] This compound was prepared in 43% yield (10.3 g) according to the Representative Procedure from 3-methyl-2-cyclohexenone (10.0 g, 90 mmol): ^1H NMR ($CDCl_3$, Me_4Si) δ 1.95–2.0 (m, 2H), 2.26 (s, 3H), 2.5–2.65 (m, 4H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 21.93, 31.86, 33.97, 36.10, 106.65, 166.76, 191.09.

2-Iodo-5,5-dimethyl-2-cyclohexenone. This compound was prepared in 59% yield (14.8 g) according to the Representative Procedure from 5,5-dimethyl-2-iodo-2-cyclohexenone (13.3 g, 100 mmol): ^1H NMR ($CDCl_3$, Me_4Si) δ 1.07 (s, 6H), 2.38 (d, J=4.5 Hz, 2H), 2.50 (s, 2H), 7.65 (t, J=4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 27.87, 34.29, 43.66, 50.53, 102.30, 157.22, 192.20.

Pd-catalyzed alkynylation of 2-iodo-2-cyclohexen-1-one with alkynylzinc bromides

2-(1-Hexynyl)-2-cyclohexen-1-one. *Representative Procedure A.* A solution of *n*-BuC≡CLi (1.3 mmol) in THF (5 mL) was prepared by adding *n*-BuLi (2.5 M in hexanes, 0.52 mL, 1.3 mmol) to 1-hexyne (107 mg, 1.3 mmol) in THF at −78°C (acetone/dry-ice bath). After warming the reaction mixture to 0°C by immersing it in an ice/water bath, a solution of anhydrous $ZnBr_2$ (293 mg, 1.3 mmol) in 5 mL of THF was added via cannula, and the resultant mixture was warmed to 23°C and stirred for 30 min. The solvent was evaporated through water aspirator, and 5 mL of dry DMF was added. In a separate 25-mL round bottom flask was placed $Pd(dba)_2$ (29 mg, 0.05 mmol), trisfurylphosphine (TFP) (23 mg, 0.1 mmol) and 5 mL of DMF. The mixture was stirred for 5–10 min until it turned clear. To this were added sequentially 2-iodo-2-cyclohexen-1-one (222 mg, 1 mmol) and the mixture containing the organozinc reagent prepared above. After 30 min, the reaction mixture was diluted with ether and quenched with aqueous NH_4Cl. After extraction with ether, the combined organic layers were washed with water and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was analyzed by NMR spectroscopy using CH_2Br_2 as an internal standard which indicated the formation of the title compound in 90% yield: ^1H NMR ($CDCl_3$) δ 0.91 (t, J=7.0 Hz, 3H), 1.3–1.6 (m, 4H), 1.9–2.1 (m, 2H), 2.3–2.5 (m, 6H), 7.19 (t, J=4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.64, 19.14, 21.98, 22.53, 26.35, 30.74, 38.13, 75.01, 93.26, 125.49, 153.25, 196.15; IR ($CDCl_3$) 2951, 2206 cm^{-1}; HRMS calculated for $C_{12}H_{16}O$: 176.1201; found: 176.1215. This representative procedure was also used in the synthesis of (±)-harveynone[18] and (±)-tricholomenyn A[19] (vide infra).

Procedure B. This experiment was carried out as described

above except that the solvent separation was omitted. The reaction was slower, requiring 1 h at 23°C. The yield of the desired product was 45% by NMR spectroscopy.

2-(3-Methyl-3-buten-1-ynyl)-2-cyclohexen-1-one. This compound was prepared according to Representative Procedure A in 87% yield (139 mg) using 2-methyl-1-buten-3-yne (86 mg, 1.3 mmol) and 2-iodo-2-cyclohexen-1-one (222 mg, 1 mmol): ^{1}H NMR ($CDCl_3$) δ 1.93 (t, J=1.0 Hz, 3H), 2.05 (quint, J=8.0 Hz, 2H), 2.4–2.6 (m, 4H), 5.2–5.3 (m, 1H), 5.3–5.4 (m, 1H), 7.28 (t, J=4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.42, 23.37, 26.48, 38.12, 82.78, 93.23,122.57, 125.20, 126.49, 154.08, 195.56; MS (CI, 70 eV) 161 (M^++1).

(1*R,4*S**,5*R**, 6*S**)-4-(*tert*-Butyldimethylsilyloxy)-5,6-epoxy-2-cyclohexen-1-ol.** The title compound was prepared according to the literature procedure[16f] in 5 steps (starting from benzoquinone) in 21% overall yield: ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 3H), 0.16 (s, 3H), 0.93 (s, 9H), 2.65 (d, J=11.0 Hz, 1H), 3.3–3.4 (m, 1H), 3.5–3.6 (m, 1H), 4.4–4.5 (m. 1H), 4.50 (dd, J=2.0, 11.0 Hz, 1H), 5.6–5.65(m, 2H); ^{13}C NMR ($CDCl_3$) δ −4.72, −4.55, 18.15, 25.72 (3C), 54.33, 56.44, 62.88, 64.02, 126.66, 127.30; IR ($CDCl_3$) 3426, 2951, 2926 cm^{-1}; MS (CI, 70 eV) 243 (M^++1).

(4*S,5*R**,6*R**)-4-(*tert*-Butyldimethylsilyloxy)-5,6-epoxy-2-cyclohexen-1-one.**[16f] A mixture of the alcohol prepared in the previous experiment (1.26 g, 5.2 mmol), PCC (1.68 g, 7.8 mmol) and 2 g of Celite in 50 mL of CH_2Cl_2 were stirred at 23°C. The reaction was monitored by TLC. After 2 h, the reaction mixture was diluted with ether and filtered through a plug of SiO_2. The solvent was evaporated in vacuo. Purification by flash chromatography gave 1.1 g (88%) of the enone as colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 3H), 0.19 (s, 3H), 0.95 (s, 9H), 3.4–3.5 (m, 1H), 3.6–3.7 (m, 1H), 4.66 (d, J=5.0 Hz, 1H), 5.97 (dd, J=1.5, 11.0 Hz, 1H), 6.5–6.6 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −4.07, −3.92, 18.67, 26.23 (3C), 53.85, 58.95, 64.19, 126.80, 144.89, 193.73; MS (CI, 70 eV) 241 (M^++1).

(4*S,5*R**,6*R**)-4-(*tert*-Butyldimethylsilyloxy)-5,6-epoxy-2-iodo-2-cyclohexen-1-one.**[16f] To a mixture of the compound obtained above (0.6 g, 2.5 mmol) in 5 mL of pyridine and 5 mL of CCl_4 mixture was added dropwise at 0°C I_2 (1.6 g, 6.25 mmol) dissolved in 10 mL of pyridine and CCl_4 (1/1). The mixture was stirred at 0°C until TLC analysis showed the disappearance of the starting material. It was then partitioned between Et_2O and 1 M HCl. The organic layer was washed with another portion of 1 M HCl and saturated $Na_2S_2O_3$ (2×), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography gave the desired product in 94% yield (0.86 g) as a light yellow-green solid: mp 72–73°C; ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 3H), 0.19 (s, 3H), 0.92 (s, 9H), 3.6–3.7 (m, 1H), 3.7–3.8 (m, 1H), 4.60 (d, J=5.0 Hz, 1H), 7.29 (dd, J=2.0, 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −4.16, −3.97, 18.63, 26.13 (3C), 52.24, 58.76, 66.65, 102.44, 153.14, 188.07; IR ($CDCl_3$) 2954, 1696 cm^{-1}; MS (CI, 70 eV) 367 (M^++1).

(4*S,5*R**,6*R**)-4-(*tert*-Butyldimethylsilyloxy)-5,6-epoxy-2-(3-methyl-3-buten-1-ynyl)-2-cyclohexen-1-one.**[16f] The compound was prepared according to the representative Procedure A in 73% yield (111 mg) using 2-methyl-1-buten-3-yne (66 mg, 1 mmol) and the iodoenone (183 mg, 0.5 mmol) prepared above: ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 3H), 0.16 (s, 3H), 0.92 (s, 9H), 1.9–2.0 (m, 3H) 3.5–3.6 (m, 1H), 3.6–3.7 (m, 1H), 4.74 (d, J=5.0 Hz, 1H), 5.30 (s, 1H), 5.40 (s, 1H), 6.65 (dd, J=2.5, 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −4.69, −4.45, 18.11, 23.08, 25.64 (3C), 53.38, 57.98, 63.79, 81.50, 95.16, 122.30, 123.67, 126.06, 145.73, 190.02; IR ($CDCl_3$) 2955, 2930, 2886, 1700 cm^{-1}; MS (CI, 70 eV) 305 (M^++1).

(4*S,5*R**,6*R**)-5,6-Epoxy-4-hydroxy-2-(3-methyl-3-buten-1-ynyl)-2-cyclohexen-1-one ((±)-Harveynone).**[23] The TBS ether prepared above (40 mg, 0.13 mmol) was treated with 48% HF in acetonitrile (v/v 1/50) at 23°C for 2 h and worked up as usual. Flash column chromatography (7/3 hexanes–EtOAc) gave the desired compound (20 mg) in 80% yield as a yellow oil: ^{1}H NMR ($CDCl_3$) δ1.94 (s, 3H), 3.30 (d, J=11.0 Hz, 1H), 3.57 (d, J=4.0 Hz, 1H), 3.8–3.9 (m, 1H), 4.7–4.8 (m, 1H), 5.3–5.4 (m, 1H), 5.4–5.5 (m, 1H), 6.85 (dd, J=2.5, 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.02, 53.55, 57.64, 63.18, 81.18, 95.90, 122.68, 124.15, 125.91, 146.18, 191.52; IR ($CDCl_3$) 3455, 2206, 1686 cm^{-1}; MS (CI, 70 eV) 191 (M^++1).

(4*R,5*S**,6*S**)-4-(*tert*-Butyldimethylsilyloxy)-5,6-epoxy-2-(7-methyl-3-methylene-6-octene-1-ynyl)-2-cyclohexen-1-one.**[16f] This compound was prepared according to the Representative Procedure A in 80% yield (148 mg) using 2-(4-methyl-3-pentenyl)-1-buten-3-yne[3b] (134 mg, 1 mmol) and (4*S**, 5*R**, 6*R**)-4-(*tert*-butyldimethylsilyloxy)-5,6-epoxy-2-iodo-2-cyclohexen-1-one (183 mg, 0.5 mmol): ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 3H), 0.16 (s, 3H), 0.90 (s, 9H), 1.59 (s, 3H), 1.65 (s, 3H), 2.1–2.3 (m,4H), 3.5–3.6 (m, 1H), 3.6–3.7(m, 1H), 4.71 (d, J=5.5 Hz, 1H), 5.0–5.1 (m, 1H), 5.28 (d, J=1.5 Hz, 1H), 5.40 (d, J=1.5 Hz, 1H), 6.65 (dd, J=2.5, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −4.70, −4.48, 17.69, 18.08, 25.62 (3C), 26.64, 37.06, 53.35, 57.95, 63.77, 82.39, 94.51, 122.35, 122.84, 123.14, 130.72, 132.27, 145.51, 189.87; IR ($CDCl_3$) 2955, 2929, 2858,1700 cm^{-1}; MS (CI, 70 eV) 373 (M^++1).

(4*R,5*S**,6*S**)-5,6-Epoxy-4-hydroxy-2-(7-methyl-3-methylene-6-octene-1-ynyl)-2-cyclohexen-1-one.**[23] The TBS ether obtained above (100 mg, 0.27 mmol) was treated with 48% HF in acetonitrile (v/v 1/50) at 23°C for 2 h and worked up as usual. Flash column chromatography (7/3 hexanes–EtOAc) gave the desired compound (61 mg) in 88% yield as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 3H),1.68 (s, 3H), 2.2 (m, 4H), 3.32 (bs, 1H), 3.55 (dd, J=1.0, 3.5 Hz, 1H), 3.8–3.9 (m,1H), 4.75 (d, J=5.5 Hz, 1H), 5.0–5.2 (m, 1H), 5.3–5.4 (m, 1H), 5.4–5.5 (m, 1H), 6.86 (dd, J=2.5, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.78, 25.71, 26.64, 37.00, 53.51, 57.69, 63.21, 81.98, 95.34, 122.68, 123.03, 123.50, 130.52, 132.48, 146.16, 191.68; IR ($CDCl_3$) 3464, 2967, 2202, 1684 cm^{-1}; MS (CI, 70 eV) 259 (M^++1).

(4*R,5*S**,6*S**)-4-Acetoxy-5,6-epoxy-2-(7-methyl-3-methylene-6-octene-1-ynyl)-2-cyclohexen-1-one ((±)-Tricholomenyn A).**[16f] The above obtained alcohol (50 mg, 0.2 mmol) was treated with DCC (0.62 g, 0.3 mmol),

DMAP (5 mg, cat.) and acetic acid (30 μl, 5 mmol) in 3 mL CH_2Cl_2 at 0°C and worked up as usual. Flash column chromatography (9/1 hexanes–EtOAc) gave (±)-tricholomenyn A (47 mg) in 81% yield: ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 3H), 1.68 (s, 3H), 2.14 (s, 3H), 2.22 (m, 4H), 3.60 (dd, *J*=1.0, 3.5 Hz, 1H), 3.7–3.8 (m, 1H), 5.0–5.2 (m, 1H), 5.34 (d, *J*=1.5 Hz, 1H), 5.45 (d, *J*=2.0 Hz, 1H), 5.82 (ddd, *J*=1.5, 1.5, 5.5 Hz, 1H), 6.75(dd, *J*=2.5, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.75, 20.64, 25.69, 26.66, 36.99, 52.95, 54.75, 64.17, 81.92, 95.94, 123.06, 123.49, 125.05, 130.55, 132.43, 140.36, 169.65, 189.45; IR ($CDCl_3$) 2968, 1742, 1703 cm^{-1}; MS (CI, 70 eV) 301 (M^++1).

Pd-catalyzed alkylation of α-iodoenones with alkylzincs

2-(*n*-Hexyl)-2-cyclopeten-1-one. *Representative Procedure A.* A three-necked 50-mL flask equipped with a septum inlet, magnetic stirring bar, a thermometer, and a mercury bubbler was charged with $ZnBr_2$ (0.38 g, 1.68 mmol) which was then flame dried at ≤1 mmHg and flushed with Ar. To this were added 3 mL of THF and *n*-hexylmagnesium bromide (1.56 mL, 2.0 M in Et_2O) at −78°C. The mixture was allowed to reach 0°C. A solution of 2-iodo-2-cyclopenten-1-one (0.50 g, 2.40 mmol), $Pd(PPh_3)_2Cl_2$ (0.08 g, 0.05 equiv. to enone) in 10 mL of DMF was canulated into the above-prepared mixture. The reaction mixture was stirred for 2 h in a water bath, quenched with aqueous NH_4Cl, and extracted with Et_2O. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (1/10 to 1/3 EtOAc–hexane) provided the desired cross coupled product in 81% yield (0.32 g, 85% by GLC); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.88 (t, *J*=6.5 Hz, 3H), 1.2–1.6 (m, 8H), 2.15 (t, *J*=6.8 Hz, 2H), 2.3–2.45 (m, 2H), 2.5–2.6 (m, 2H), 7.31 (m, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 14.10, 22.61, 24.81, 26.46, 27.74, 29.11, 31.63, 34.63, 146.54, 157.32, 210.09; IR (neat) 1738, 1704, 1632, 1444, 1406 cm^{-1}; HRMS calcd for $C_{11}H_{18}O$ 166.1358, found 166.1359.

2-Ethyl-2-cyclopenten-1-one.[34] This compound was prepared in 69% yield (0.36 g, 85 % by GLC) according to the Representative Procedure A except that commercially available Et_2Zn was used: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.09 (t, *J*=7.4 Hz, 3H), 2.10 (q, *J*=7.4 Hz, 2H), 2.3–2.45 (m, 2H), 2.5–2.6 (m, 2H), 7.30 (t, *J*=2.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 11.95, 17.97, 26.30, 34.55, 147.78, 156.54, 209.89; IR (neat) 1702, 1632, 1444, 1349, 1252 cm^{-1}.

2-(*n*-Butyl)-2-cyclopenten-1-one.[35] This compound was prepared according to the Representative Procedure A from *n*-butylmagnesium chloride (1.56 mL, 2.0 M in THF), $ZnBr_2$ (0.38 g, 1.68 mmol), 2-iodo-2-cyclopenten-1-one (0.50 g, 2.40 mmol), $Pd(PPh_3)_2Cl_2$ (0.08 g, 0.05 equiv. to enone), THF (8 mL), DMF (10 mL) in 79% yield (0.30 g, 88% by GLC): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.91 (t, *J*=7.0 Hz, 3H), 1.2–1.6 (m, 2H), 2.1–2.25 (m, 2H), 2.35–2.5 (m, 2H), 2.5–2.65 (m, 2H), 7.30 (t, *J*=1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.81,22.45, 24.44, 26.39, 29.84, 34.56, 146.47, 157.25, 210.09; IR (neat) 1704, 1632, 1466, 1444 cm^{-1}; HRMS calcd for $C_9H_{14}O$ 138.1045, found 138.1046.

2-Isobutyl-2-cyclopenten-1-one. This compound was prepared according to the Representative Procedure using isobutylmagnesium bromide (1.56 mL, 2.0 M in Et_2O) in 73% yield (0.24 g, 85% by GLC): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.88 (d, *J*=6.6 Hz, 6H), 1.7–1.95 (m, 1H), 2.07 (d, *J*=6.9 Hz, 2H), 2.3–2.45 (m, 2H), 2.55–2.65 (m, 2H), 7.32 (t, *J*=2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 22.28, 22.38, 26.32, 26.82, 33.74, 34.39, 145.11, 145.40, 210.00; IR (neat) 1702, 1630, 1466, 1444 cm^{-1}; HRMS calcd for $C_9H_{14}O$ 138.1045, found 138.1044.

2-(*n*-Butyl)-3-methyl-2-cyclopenten-1-one.[35] This compound was prepared according to the Representative Procedure A using *n*-butylmagnesium chloride (6.24 mL, 2.0 M in THF) and 2-iodo-3-methyl-2-cyclopenten-1-one (2.13 g, 9.60 mmol) in 66% yield (0.96 g, 76% by GLC): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.89 (t, *J*=6.6 Hz, 3H), 1.2–1.5 (m, 4H), 2.06 (s, 3H), 2.17 (t, *J*=6.8 Hz, 2H), 2.3–2.4 (m, 2H), 2.45–2.6 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.51, 16.80, 22.31, 22.36, 30.19, 31.08, 33.91, 140.20, 169.68, 209.15; IR (neat) 1696, 1646, 1441, 1385 cm^{-1}; MS (EI, relative intensity), *m/e* 152 (M^+) (26), 137 (45), 123 (18), 110 (100), 95 (27).

2-(*n*-Butyl)-4-methyl-2-cyclopenten-1-one. This compound was prepared according to the Representative Procedure A using *n*-butylmagnesium chloride (6.24 mL, 2.0 M in THF) and 2-iodo-4-methyl-2-cyclopenten-1-one (2.13 g, 9.60 mmol) in 59% yield (0.86 g, 67% by GLC): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.91 (t, *J*=7.0 Hz, 3H), 1.17 (d, *J*=7.1 Hz, 3H), 1.2–1.6 (m, 4H), 1.93 (dd, *J*=2.0, 18.7 Hz, 1H), 2.15 (t, *J*=7.5 Hz, 2H), 2.61 (dd, *J*=6.4, 18.7 Hz, 1H), 2.8–3.0 (m, 1H), 7.19 (d, *J*=2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.41, 19.96, 22.02, 23.84, 29.43, 32.85, 42.85, 144.83, 162.06, 209.00; IR (neat) 1738, 1704, 1459 cm^{-1}; HRMS calcd for $C_{10}H_{16}O$ 152.1098, found 152.1097.

2-(*n*-Butyl)-2-cyclohexen-1-one.[36] This compound was prepared according to the Representative Procedure A using *n*-butyllithium (2.50 mL, 2.5 M in hexane) and 2-iodo-2-cyclohexen-1-one (1.07 g, 4.80 mmol) in 63% yield (0.46 g, 75% by GLC): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.89 (t, *J*=6.8 Hz, 3H), 1.15–1.5 (m, 4H), 1.97 (tt, *J*=6.1, 13.0 Hz, 2H), 2.17 (t, *J*=6.8 Hz, 2H), 2.3–2.5 (m, 4H), 6.70 (t, *J*=4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.83, 22.39, 23.08, 25.96, 29.13, 30.67, 38.51, 139.82, 144.71, 199.46; IR (neat) 1647, 1459, 1376 cm^{-1}.

Pd-catalyzed α-benzylation of α-iodoenones

2-Benzyl-2-cyclopenten-1-one.[37] *Representative Procedure B.* A dry, three-necked 50 mL flask equipped with an Ar inlet, a mercury bubbler, a magnetic stirring bar, a reflux condenser, and a thermometer were charged with Zn dust (0.25 g, 3.80 mmol), THF (1 mL), and 1,2-dibromoethane (13 μL, 0.04 equiv. to Zn). This suspension was heated to reflux for 10 min and then cooled to 0°C. A solution of benzyl bromide (0.37 mL, 3.10 mmol) in THF (6 mL) was added dropwise, and the mixture was stirred at 0°C for 3 h. The supernatent solution of benzylzinc bromide thus prepared was canulated to a one-necked 25 mL flask containing 2-iodo-2-cyclopenten-1-one (0.50 g, 2.40

mmol) and $Pd(PPh_3)_2Cl_2$ (0.08 g, 0.05 equiv. to enone) in DMF (10 mL) kept at 0°C. The resultant mixture was stirred at 23°C for 2 h, quenched with aqueous NH_4Cl, extracted with Et_2O. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (1/1 to 1/3 EtOAc–hexane) provided the title compound in 74% yield (0.30 g, 82% by GLC: ^1H NMR ($CDCl_3$, Me_4Si) δ 2.25–2.35 (m, 2H), 2.4–2.5 (m, 2H), 3.44 (s, 2H), 7.05–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 25.90, 30.75, 33.94, 125.66, 127.90 (2C), 128.30 (2C), 138.33, 145.19, 158.30, 208.21; IR (neat) 3062, 3028, 1700, 1632, 1602, 1496 cm^{-1}; HRMS calcd for $C_{12}H_{12}O$ 172.0888, found 172.0891.

2-Benzyl-2-cylcohexenone. This compound was prepared according to the Representative Procedure B from 2-iodo-2-cyclohexenone (0.22 g, 1.0 mmol). Analysis of the ^1H NMR spectrum of the crude product mixture indicated a 94% yield of the title compound.[38] Flash chromatography afforded the product as a light yellow oil: ^1H NMR ($CDCl_3$, Me_4Si) δ 1.9–2.0 (m, 2H), 2.25–2.4 (m, 2H), 2.43 (t, J=6.15 Hz, 2H), 3.51 (s, 2H), 6.54 (t, J=4.3 Hz, 1H), 7.2–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 23.56, 26.60, 35.94, 39.00, 126.57, 128.88, 129.69, 139.98, 14017, 147.00, 199.48; IR (neat) 3027, 2924, 1709, 1672 cm^{-1}; MS (EI, 70eV) m/z (relative intensity) 186 (M^+, 100), 158 (31), 129 (67), 115 (45), 105 (11), 91 971), 77 (18), 65 (29), 51 (41).

2-Benzyl-3-methyl-2-cyclohexenone. This compound was prepared according to the Representative Procedure B from 2-iodo-3-methyl-2-cyclohexenone (0.62 g, 2.6 mmol) in 72% yield by NMR. Flash chromatography afforded the title compound[39] as a light yellow oil: ^1H NMR ($CDCl_3$, Me_4Si) δ 1.9–2.0 (m, 5H), 2.35–2.45 (m, 4H), 3.68 (s, 2H), 7.1–7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 21.74, 22.15, 30.54, 32.91, 37.69, 125.54, 127.87, 128.16, 134.61, 140.53, 157.07, 198.47; IR (neat) 3060, 3024, 2925, 1658 cm^{-1}; MS (EI, 70 eV) *m/z* (relative intensity) 200 (M^+, 63), 185 934), 171 (19), 129 (100), 91 (48), 65 (17), 55 (38).

In another run, benzylzinc bromide was treated with one molar equiv. of $MgBr_2$. The reaction run under otherwise the same conditions did not yield the title compound in more than a trace, if any, quantity.

2-Benzyl-5,5-dimethyl-2-cyclohexenone. This compound was prepared according to the Representative Procedure B from 5,5-dimethyl-2-iodo-2-cyclohexenone (1.35 g, 5.4 mmol) in 71% yield by NMR. Flash chromatography afforded the product[40] as a light yellow oil: ^1H NMR ($CDCl_3$, Me_4Si) δ 1.02 (s, 6H), 2.20 (d, J=4.2 Hz, 2H), 2.29 (s, 2H), 3.54 (s, 2H), 6.44 (t, J=4.2 Hz, 1H), 7.15–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 27.95, 33.72, 34.84, 39.76, 51.65, 125.70, 128.03, 128.73, 138.05, 139.41, 143.78, 198.50; IR (neat) 3024, 2954, 1676 cm^{-1}; MS (EI, 70 eV) *m/z* (relative intensity) 214 (M^+, 100), 199 (5), 158 (71), 129 (42), 115 (28), 105 (17), 91 (81), 65 (16).

Pd-catalyzed α-homobenzylation, α-homoallylation, and α-homopropargylation of α-iodoenones

5,5-Dimethyl-2-(2′-phenylethyl)-2-cyclohexenone. To a solution of 2-bromoethylbenzene (1.20 g, 6.5 mmol) in THF (5 mL) were added magnesium powder (0.32 g, 13.1 mmol) and flame-dried zinc bromide (1.7 g, 8.7 mmol). The mixture was stirred with gentle warming. The reaction of 2-phenylethylzinc bromide thus generated with 5,5-dimethyl-2-iodo-2-cyclohexenone (0.69 g, 2.6 mmol) in the presence of $Pd(PPh_3)_2Cl_2$ (52 mg, 0.07 mmol) in DMF (15 mL) and the workup were carried out according to the Representative Procedure A. Analysis of the ^1H NMR spectrum of the crude product indicated an 83% yield of the titled compound.[40] Flash chromatography afforded the product as a light yellow oil: ^1H NMR ($CDCl_3$, Me_4Si) δ 0.93 (s, 6H), 2.10 (d, J=4.3 Hz, 2H), 2.20 (s, 2H), 2.4–2.7 (m, 4H), 6.39 (t, J=4.3 Hz, 1H), 7.05–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 28.23, 31.35, 34.83, 40.09, 52.09, 125.76, 128.20, 128.51, 137.75, 141.82, 143.59, 199.50; IR (neat) 3027, 2958, 1710, 1672 cm^{-1}; MS (EI, 70 eV) *m/z* (relative intensity) 228 (M^+, 47), 213 (1), 105 (17), 91 (100), 71 (23), 53 (36).

2-(3′-Butenyl)-2-cyclopentenone. This compound was prepared by the reaction of 2-iodo-2-cyclopentenone (1.04 g, 5.0 mmol) with 3-butenylzinc bromide (10 mL, 7 mmol), prepared in situ from 4-bromo-1-butene (1.35 g, 10 mmol), Mg (0.37 g, 15 mmol), a catalytic amount of I_2 and $ZnBr_2$ (2.3 g, 10 mmol) in THF (15 mL) at 23°C for 6 h, in the presence of $Cl_2Pd(TFP)_2$ (160 mg, 0.25 mmol) and DMF (5 mL). Analysis of the ^1H NMR spectrum of the crude product indicated a 36% yield of the title compound. Flash chromatography afforded the product as a light yellow oil: ^1H NMR ($CDCl_3$, Me_4Si) δ 2.1–2.25 (m, 4H), 2.3–2.35 (m, 2H), 2.45–2.5 (m, 2H), 4.9–5.0 (m, 2H), 5.65–5.8 (m, 1H), 7.2–7.3 (m, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 22.48, 23.99, 26.39, 31.58, 34.47, 115.03, 137.65, 145.46, 157.73, 209.78; IR (neat) 3077, 2920, 1702, 1633 cm^{-1}; HRMS calcd for $C_9H_{12}O$ 136.0888, found 136.0882.

5,5-Dimethyl-2-(3′-octynyl)-2-cyclohexenone. This compound was prepared from 5,5-diemthyl-2-iodo-2-cyclohexenone (1.58 g, 6.3 mmol), 3-octynylzinc bromide, generated in situ by treating 1-bromo-3-octyne (1.44 g, 7.6 mmol) in THF (5 mL) with I_2 (20 mg, 0.08 mmol), magnesium powder (0.19 g, 7.6 mmol), and flame-dried zinc bromide (1.71 g, 7.6 mmol) at 23°C for 6 h, in the presence of $Pd(PPh_3)_2Cl_2$ (52 mg, 0.07 mmol) in DMF (10 mL). Analysis of the ^1H NMR spectrum of the crude product indicated a 41% yield of the title compound.[40] flash chromatography afforded the product as a light yellow oil: ^1H NMR ($CDCl_3$, Me_4Si) δ 0.85–0.9 (m, 4H), 1.03 (s, 6H), 1.35–1.45 (m, 5H), 2.2–2.35 (m, 8H), 650 (t, J=4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.59, 18.13, 18.34, 21.83, 28.19, 29.09, 31.17, 34.00, 40.13, 51.98, 79.37, 81.09, 136.97, 144.16, 199.25; IR (neat) 2961, 1713, 1174, 916, 733 cm^{-1}; MS (CI, 70 eV) *m/z* (relative intensity) 232 (M^+, 54) 217 (20), 203 923), 190 (78), 189 (92), 133 (88), 119 (74), 105 (94), 91 (100).

2-(4-Trimethylsilyl-3-butynyl)-2-cyclohexen-1-one. In a round bottom flask were placed zinc dust (0.325 g, 5 mmol) and DMF (5 mL). The zinc dust was activated with 1,2-dibromoethane (5%) and TMSCl (2%). 4-Iodo-1-trimethylsilyl-1-butyne (0.252 g, 2 mmol) was added, and the flask was placed into an oil bath (50°C) until GLC

analysis showed the complete consumption of the iodide. In another round bottom flask were placed $Pd(dba)_2$ (29 mg, 0.05 mmol), TFP (23 mg, 0.1 mmol) and 3 mL of DMF. The resultant mixture was stirred for 5 min until it turned clear. To this were added sequentially 2-iodo-2-cyclohexen-1-one (0.222 g, 1 mmol) and the organozinc reagent prepared above. After one hour, TLC analysis showed the disappearance of the starting material. The reaction mixture was quenched with aqueous NH_4Cl and extracted with ether. The combined organic layers were washed with H_2O, dried over $MgSO_4$ and.concentrated. The product was purified by flash column chromatography (95/5 hexanes–EtOAc) and isolated as an oil (134 mg) in 61% yield (80% by GLC): ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 9H) 1.95 (q, J=6.5 Hz, 2H) 2.2–2.4 (m, 8H) 6.75 (t, J=4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 0.68 (3C), 19.87, 23.63, 26.57, 29.49, 38.97, 85.89, 107.39, 138.17, 147.34, 199.60; MS (CI, 70 eV) 221 (M^++1).

Reactions of allylzinc and propargylzinc derivatives with α-iodoenones in the presence of a Pd–phosphine complex

1-Allyl-2-iodo-2-cyclopenten-1-ol. Diallylzinc was generated in situ by treating commercially available allylmagnesium chloride (1.56 mL, 2.0 M in THF, 3.12 mmol) with dry $ZnBr_2$ (0.38 g, 1.68 mmol) and reacted with 2-iodocyclopenten-1-one (0.50 g, 2.40 mmol) in the presence of $Cl_2Pd(PPh_3)_2$ (0.08 g, 0.05 equiv. of the enone) in THF (8 mL) and DMF (10 mL). The reaction produced the title compound in 88% yield (0.53 g): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.85–2.1 (m, 2H), 2.15–2.55 (m, 5H), 5.1–5.3 (m, 2H), 5.6–5.9 (m, 1H), 6.25 (t, J=2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 32.81, 33.03, 44.53, 86.00, 106.53, 118.98, 132.54, 141.70; IR (neat) 3396 (br.), 3074, 1640, 1604, 1436, 1316, 1066 cm^1; HRMS calcd for $C_8H_{11}OI$ 249.9855, found 249.9854.

1-Propargyl-2-iodo-2-cyclopenten-1-ol.[41] The reaction of propargylzinc bromide, generated in situ by treating propargyl bromide (80% wt. in toluene, 0.70 mL, 6.2 mmol) with Zn dust (0.94 g, 14.4 mmol), with 2-iodo-2-cyclopenten-1-one (1.00 g, 4.80 mmol) in the presence of $Pd(PPh_3)_2Cl_2$ (0.17 g, 0.05 equiv. to enone) in THF (16 mL), DMF (20 ML) was run at 0°C in a manner similar to that with allylzinc derivatives. The reaction provided the title compound in 80% yield (0.95 g, 89% by NMR): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.9–2.15 (m, 2H), 2.25–2.65 (m, 5H), 2.69 (2, 1H), 6.30 (t, J=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 30.54, 32.86, 33.53, 70.34, 79.37, 85.66, 104.16, 142.62; IR (neat) 3385 (b.), 3295, 2120, 1606, 1423, 1319, 1063 cm^{-1}; HRMS calcd for $C_8H_9OI-H_2O$ 230.9671, found 230.9669.

Conjugate reduction of α-alkyl-α,β-unsaturated enones

A Pd-catalyzed procedure reported by Keinan[33] was used in the following experiments.

2-Butyl-cyclopentan-1-one.[42] 2-Butyl-2-cyclopenten-1-one (60 mg, 0.43 mmol) was reduced as reported in the literature[33] with $ZnCl_2$ (60 mg, 0.44 mmol), Ph_2SiH_2 (160 μL, 0.86 mmol), and Me_3SiCl (60 μL, 0.44 mmol) in $CHCl_3$ (2 mL) in the presence of $Pd(PPh_3)_4$ (10 mg, 0.02 equiv. to enone). The reaction mixture was stirred at 23°C for 2 h in open air, quenched with aqueous NH_4Cl, extracted with $CHCl_3$, washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (1/20 to 1/5 EtOAc–hexane) provided the title compound in 81% yield (49 mg, 86% by GLC): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.92 (t, J=7.0 Hz, 3H), 1.15–2.4 (m, 13H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.92, 21.81, 22.40, 29.56, 29.61, 29.77, 38.10, 49.22, 221.54; IR (neat) 1729, 1076 cm^{-1}.

2-Benzylcyclopentan-1-one.[43] This compound was prepared as above from 2-benzyl-2-cyclopenten-1-one (50 mg, 0.29 mmol) in 98% yield (49 mg, quantitative by GLC): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.4–1.85 (m, 2H), 1.85–2.2 (m, 3H), 2.35 (m, 2H), 2.53 (dd, J=9.5, 13.6 Hz, 1H), 3.15 (dd, J=3.9, 13.6 Hz, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 20.48, 29.07, 35.51, 38.13, 50.96, 126.08, 128.34 (2 C), 128.34 (2 C), 139.93, 220.12; IR (neat) 3051, 3009, 1739, 1496, 1453, 1154 cm^{-1}; MS (EI, relative intensity) *m/e* 174 (M^+) (75), 156 (7), 146 (21), 117 (43), 91 (100).

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