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Copper-Catalyzed Conjugate Additions of Organozirconocenes. Synthetic and Mechanistic Studies.

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Abstract: In the presence of 3-10 mol % of Cu(I) salts such as CuBr·SMe_2 or CuCN, alkylzirconocenes add readily to α,β-unsaturated ketones, aldehydes, and sulfones. The reaction yield is sensitive to the presence of Lewis acids and bases. Steric hindrance as well as a broad range of functional groups are tolerated in the conjugate addition process. Unsaturated *N*-acyl oxazolidinones give high diastereoselectivities for the formation of the new asymmetric carbon. The resulting zirconium enolates can be used for tandem aldol addition reactions to aldehydes. Depending on the type of copper salt used, slow or fast formation of copper mirror occurs, but no intermediate copper species is detected spectroscopically. Therefore, a mechanism involving enone complexation by the Lewis-acidic zirconocene followed by inner-sphere transfer of the alkyl substituent to chelated Cu(I) is proposed.

Introduction

Alkenes and alkynes are readily hydrometalated with zirconocene hydrochloride (Schwartz' reagent).[1] The resulting alkyl and alkenyl zirconocenes have been extensively used in synthetic transformations.[2] Deuterolysis of organozirconocenes is a useful tool for the introduction of deuterium labels,[3] and treatment with halogens provides halides in excellent yields.[4] Oxidations convert alkylzirconium derivatives to primary and secondary alcohols.[5] Since the considerable steric crowding around the Zr atom in zirconocenes decreases its nucleophilicity, direct carbon-carbon bond forming reactions of alkyl- and alkenylzirconocenes have so far been limited to CO and isocyanide insertions,[2,6] as well as olefin and alkyne insertions,[7] additions of cationic organozirconium complexes to oxiranes[8] and aldehydes,[9] and Ni- or Pd-catalyzed cross-couplings.[10] The use of hydrozirconation products as carbanion equivalents is greatly facilitated by transmetalations to the more reactive aluminum,[11] nickel,[12] and copper derivatives.[13] Especially for the catalysis of conjugate additions as well as tandem conjugate additions - enolate trappings, alkenyl zirconocenes in combination with low-valent Ni complexes have found considerable application in organic synthesis.[14]

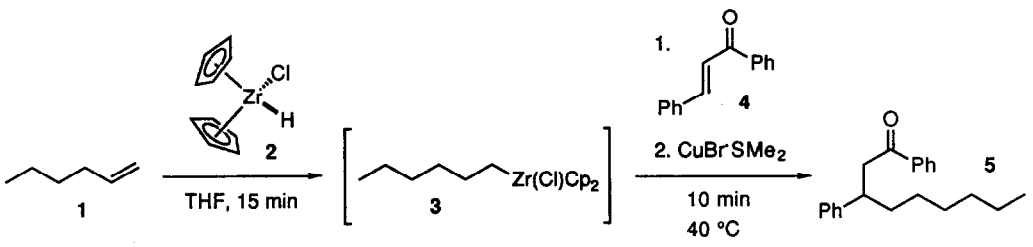
While transfer of *alkenyl* groups from zirconium to copper occurs readily,[15] early attempts to effect a transmetalation of *alkyl*zirconium species to copper or nickel salts were not successful.[12c,15a,16] In a recent communication, we have reported an *in situ* protocol for the copper(I)-

catalyzed conjugate addition of alkylzirconocenes to α,β-unsaturated carbonyl compounds.[17] This method can also be applied for the preparation of highly functionalized ketones from organozirconocenes and acyl chlorides.[18] In this paper, we present further studies on the scope of copper-catalyzed conjugate additions of alkylzirconium reagents and some mechanistic evidence for the involvement of short-lived organocopper complexes in this process.

Results and Discussion

Reaction Optimization. Addition of 1.1 equiv of zirconocene hydrochloride (**2**) to a 0.24 M solution of 1-hexene (**1**) in THF led to a rapid formation of a yellow, homogeneous solution of hexylzirconocene (Scheme I).

Scheme I



Treatment of this reaction mixture with 1.0 equiv of chalcone (**4**), followed by 10 mol % of copper bromide dimethylsulfide complex at 40 °C, induced a rapid color change to dark green. After 10 min, 37% of the 1,4-addition product **5** was detected by GC analysis. A drop in yield to 23% resulted when 5 mol % of copper catalyst was used, and no measurable conversion occurred after 30 min in the absence of copper salts.[19]

Since this facile copper-catalyzed conjugate addition of an alkylzirconocene to an enone was in stark contrast to the earlier unsuccessful transmetalation attempts,[12c,15a,16] we pursued a systematic study of the effect of additives and the nature of the copper salt on the formation of **5** (Table I).

A decrease in the reaction temperature from 40 °C to room temperature provided **5** in 44% yield after 1 h reaction time (entry 3). If, however, hexylzirconocene and the copper salt were premixed for 30 min before addition of chalcone, only 16% of product was detected (entry 4). In the presence of 3 equiv of TMSCl, the yield increased slightly from 37 to 45%, however, addition of HMPA led to a complete inhibition of the conjugate addition pathway (entries 5 & 6).[20] Similarly, an excess of Me_2S led to a considerable drop in the reaction yield (entry 7).

In our preliminary studies,[17] we had noticed that the rate of 1,4-addition of hexylzirconocene to cyclohexenone was greatly reduced if Lipshutz'[21] or Negishi's[22] protocols were used for the preparation of Schwartz reagent. In these procedures, Schwartz reagent is prepared in situ by reduction of zirconocene dichloride with $LiEt_3BH$[21] and ^tBuMgCl,[22] respectively. Hydrozirconation of alkenes with commercial[23] Cp_2ZrHCl as well as with reagent prepared from $LiAl(O^tBu)_3H$[24] or $LiAlH_4$[25] reduction of Cp_2ZrCl_2, however, resulted in alkylzirconocene that readily underwent the desired copper-catalyzed conjugate addition. In accordance with these observations,[17] we observed that the addition of chalcone and Cu(I) complex to hexylzirconocene obtained via the Lipshutz and Negishi protocols

led, even after prolonged exposure, only to a marginal formation of **5** (entries 8 & 10). Triethylborane, which is a side product in the in situ preparation of Schwartz reagent with $LiEt_3BH$, did not cause the observed inhibition of the conjugate addition process; the yield of **5** upon addition of 1 equiv of Et_3B to the standard reaction mixture actually almost doubled to 69% (entry 9). In the presence of LiCl, however, only traces of **5** were detected (entry 11). Both Li^+- and Cl^--ions inhibit product formation (entries 12 & 13). Since 1 equiv of LiCl is formed in Lipshutz' preparation of Cp_2ZrHCl, the observed sluggish addition and modest yield in the subsequent copper-catalyzed 1,4-addition of the alkyzirconocene is very likely the consequence of simultaneous reaction enhancement (Et_3B) and strong inhibition (LiCl) by the reaction side products Et_3B and LiCl. Analogously, $MgBr_2$ was found to suppress the formation of conjugate addition product, whereas $ZnCl_2$ showed a more moderate inhibitory effect (entries 14 & 15).

Aluminum alkoxide are possible impurities in the formation of Cp_2ZrHCl by reduction of the zirconocene dichloride with aluminum hydrides. Interestingly, $Al(OEt)_3$ also demonstrated rate-enhancing activity in the formation of **5** (entry 16). Optimal conditions were achieved in the presence of 1 equiv of BF_3-etherate, which provided a 74% yield of **5** after chromatographic purification. The strongly Lewis-acidic BF_3-etherate was even sufficient to promote the conjugate addition of alkylzirconocene to enone in the absence of copper(I) salts, though with considerably reduced efficiency (entries 17 & 18).

The concentration of the reactants, especially enone and alkylzirconocene, is an important parameter in the copper-catalyzed conjugate addition. In our reference reaction (entry 1), we obtained a 37% yield of **5** with a 0.24 molar solution of hexylzirconocene and chalcone. Concentrating the reaction mixture to 0.6 molar resulted in a significant increase to 65% (entry 19). In both experiments the reaction basically stopped after 10 min at 40 °C.

We also extensively investigated the effect of other copper complexes on the conjugate addition of *n*-hexylzirconocene to chalcone. Most copper salts, e.g. CuI·2LiCl,[26] CuCN·2LiCl,[27] CuI·$P(OEt_3)$,[28] CuSPh,[29] and CuCl-cyclooctadiene complex,[30] gave significantly lower yields than CuBr-dimethyl sulfide complex (entries 20-26). With CuCN, the reaction mixture remained homogenous and did not form the standard dark green precipitate that is generally formed rapidly and indicates a near completion of the reaction. Product formation continued for several hours, and after 9 h at 40 °C, 48% of **5** was detected (entry 22). The soluble Li_2CuCl_4[31] led also to a rather sluggish reaction and provided only 5% of product after 10 min at 40 °C (entry 27). Kuwajima and co-workers recently reported a facile 1,4-addition of Grignard reagents to α,β-unsaturated esters in the presence of a Cu(II)-salicylaldehyde-isopropyl amine complex.[32] In the presence of TMSCl, this catalyst proved similarly effective for the conjugate addition of *n*-hexylzirconocene to chalcone (entry 28).

If the copper-catalyzed conjugate addition of alkylzirconocenes to enones involves an initial transmetalation, the low reactivity and thermal stability of the resulting alkylcopper species could be improved by ate complex formation.[33] The preparation of mixed cuprates with MeCu and thermally highly stable lithium and magnesium bis-hexynyl cyanocuprates,[15e] however, did not lead to substantial increases in the yield of **5**, even though consistently homogenous solutions were obtained for several hours at room temperature and no copper metal precipitated during the course of the reactions (entries 29-35).

Table I. Variation of Reaction Parameters in the Copper-Catalyzed Conjugate Addition of *n*-Hexylzirconocene (3) to Chalcone (Scheme I).

entry	Cu(I) complex (mol %)	additive (equiv)	reaction time	reaction temperature [°C]	% yield of 5[a]
1	$CuBr{\cdot}SMe_2$ (10)	-	10 min	40	37
2	$CuBr{\cdot}SMe_2$ (5)	-	10 min	40	23
3	$CuBr{\cdot}SMe_2$ (10)	-	1 h	22	44
4[b]	$CuBr{\cdot}SMe_2$ (10)	-	30 min	22	16
5	$CuBr{\cdot}SMe_2$ (10)	TMSCl (3)	10 min	40	45
6	$CuBr{\cdot}SMe_2$ (10)	TMSCl (3) HMPA (3)	10 min	40	<2
7	$CuBr{\cdot}SMe_2$ (10)	Me_2S (10)	30 min	40	8
8[c]	$CuBr{\cdot}SMe_2$ (10)	-	30 min	40	13
9	$CuBr{\cdot}SMe_2$ (10)	Et_3B (1)	20 min	40	69
10[d]	$CuBr{\cdot}SMe_2$ (10)	-	1.5 h	40	15
11	$CuBr{\cdot}SMe_2$ (10)	LiCl (1)	2 h	40	<2
12	$CuBr{\cdot}SMe_2$ (10)	$LiClO_4$ (1)	20 min	40	9
13	$CuBr{\cdot}SMe_2$ (10)	Bu_4NCl (1)	1 h	40	<2
14	$CuBr{\cdot}SMe_2$ (10)	$MgBr_2$ (1)	1.5 h	40	12
15	$CuBr{\cdot}SMe_2$ (10)	$ZnCl_2$ (2)	1 h	40	21
16	$CuBr{\cdot}SMe_2$ (10)	$Al(OEt)_3$ (1)	20 min	40	61
17	$CuBr{\cdot}SMe_2$ (10)	$BF_3{\cdot}Et_2O$ (1)	20 min	40	74[e]
18	-	$BF_3{\cdot}Et_2O$ (1)	20 min	40	15
19[f]	$CuBr{\cdot}SMe_2$ (10)	-	10 min	40	65
20	$CuI{\cdot}2LiCl$ (10)	-	2 h	40	19
21	CuCN (10)	-	10 min	40	8
22	CuCN (10)	-	9 h	40	48
23	$CuCN{\cdot}2LiCl$ (10)	-	1 h	40	4
24	$CuI{\cdot}P(OEt_3)$ (10)	-	10 min	40	0
25	CuSPh (10)	-	10 min	40	0
26	CuCl·COD (10)	-	10 min	40	25
27	Li_2CuCl_4 (10)	-	10 min	40	5
28	Cu(II)-salicylimine (10)	TMSCl (3)	1 h	22	58
29	MeCu (100)	-	1 h	0	57
30	$(n\text{-}C_4H_9C{\equiv}C)_2CuCNLi_2$ (10)	-	10 min	40	25
31	$(n\text{-}C_4H_9C{\equiv}C)_2CuCN(MgBr)_2$ (10)	-	10 min	40	14
32	$(n\text{-}C_4H_9C{\equiv}C)_2CuCN(MgBr)_2$ (10)	-	4 h	22	6
33	$(n\text{-}C_4H_9C{\equiv}C)_2CuCN(MgBr)_2$ (50)	-	3 h	22	50
34	$(n\text{-}C_4H_9C{\equiv}C)_2CuCN(MgBr)_2$ (100)	-	3 h	22	55
35	$(n\text{-}C_4H_9C{\equiv}C)_2CuCN(MgBr)_2$ (100)	-	2 h	-23	14

[a]Based on enone and determined by GC analysis of the crude reaction mixture in the presence of an internal standard, unless otherwise noted. Generally, unreacted chalcone accounted for the difference in the mass balance. [b]Before addition of chalcone, the mixture of hexylzirconocene and copper salt was stirred for 30 min at 22 °C. [c]Zirconocene hydrochloride was prepared in situ according to Lipshutz' procedure.[21] [d]Zirconocene hydrochloride was prepared in situ according to Negishi's procedure.[22] [e]Yield of chromatographically purified material. [f]The concentration of *n*-hexylzirconocene was increased from 0.24 M to 0.6 M.

Mechanistic Studies. An NMR analysis of the reaction of *n*-hexylzirconocene with CuBr·SMe_2 revealed no evidence for the intermediate formation of alkylcopper species. Even though a dark green precipitate formed rapidly, the ^{13}C NMR showed only a slow and clean conversion of *n*-hexylzirconocene to *n*-hexane in $CDCl_3$ at 22 °C and in the presence of 10-100% of copper salt. The half-life of this process in THF could be estimated at approx. 12 h with 10% CuBr·SMe_2. In THF and in the presence of 1 equiv of the soluble copper salt CuI·2LiCl, the hexylzirconocene→hexane conversion occurred with a half-life of ca. 60 min. In the absence of copper salts, no decomposition of the hexylzirconocene reagent was noticed after 24 h at 22 °C. Therefore, copper(I) clearly facilitated the formal protonation of the alkyl ligand on the zirconocene. The conspicuous absence of 1-hexene in the reaction mixture can be interpreted as evidence *against* the formation of alkylcopper species via Zr→Cu transmetalation, since Whitesides and Kochi established that the thermal decomposition of alkylcopper(I) compounds with β-hydrogens affords an equimolar amount of alkene and alkane.[34] However, the degree of association of the transiently formed alkylcopper species as well as its coordination to the zirconocene complex must be taken into account. The thermal decomposition of $ZrMe_2(\eta\text{-}C_5D_5)_2$ provided MeD, and a rapid H/D exchange occurred between σ- and π-ligands, presumably involving the metal center.[35] Therefore, transiently formed zirconocene hydrides could reduce any alkylcopper species within the coordination sphere and thus mediate the observed formation of alkane and copper(0). Alternatively, outer electron sphere oxidation of the zirconocene by Cu(I) followed by H-atom abstraction is also feasible.

Interestingly, the disappearance of the characteristic signals of the *n*-hexylzirconocene species in ^{13}C NMR was greatly accelerated in the presence of both Cu(I) *and* enone. Addition of 1 equiv of chalcone to a solution of *n*-hexylzirconocene in THF, followed by 10 mol% of CuBr·SMe_2, led to the disappearance of hexylzirconocene with a half-life of 1 h. Besides some conjugate addition product, again predominantly *n*-hexane was formed in this process. A reversible transmetalation from copper to zirconium, however, appears unlikely. Addition of zirconocene dichloride to Me_2CuLi in ether at -38 °C led to the rapid formation of $Cp_2Zr(Me)Cl$ and bright yellow, insoluble MeCu (eq 1). However, no further reaction was detected even at higher temperatures. No formation of $Cp_2Zr(Me)Cl$ was detected in ^1H NMR in a mixture of MeCu and a large excess of Cp_2ZrCl_2 in ether or THF at -7 °C (eq 2).

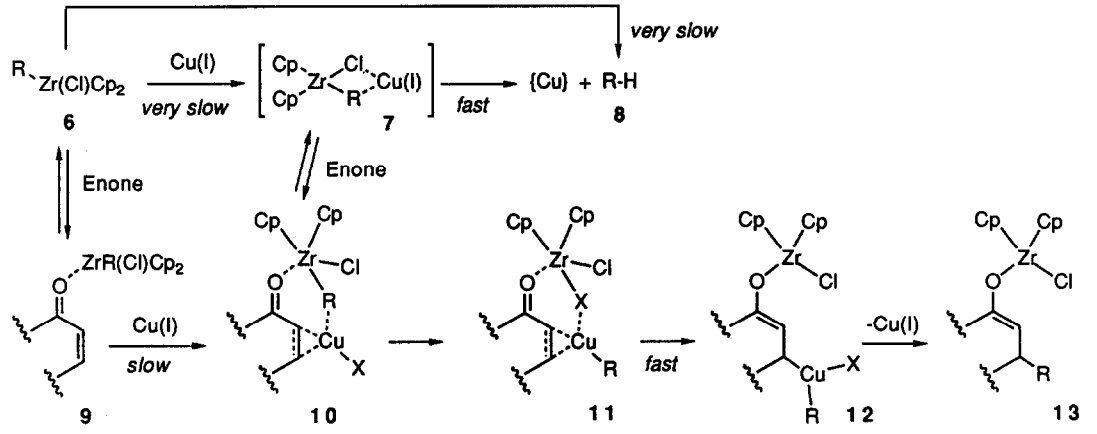
$$Cp_2ZrCl_2 + Me_2CuLi \longrightarrow Cp_2Zr(Me)Cl + MeCu + LiCl \qquad (1)$$

$$Cp_2ZrCl_2 \text{ (excess)} + MeCu \xrightarrow{-x} Cp_2Zr(Me)Cl + MeCl \qquad (2)$$

Since a Cu→Zr transmetalation, e.g. a rapid equilibrium that is trapped by addition of enone, seems to be at least kinetically unfavorable, we propose two different major pathways for the interaction between organozirconocenes and copper(I) salts in the presence or absence of enone acceptors, respectively (Scheme II). Direct decomposition of alkylzirconocene species **6** to give alkane **8** is extremely slow in the absence of Cu(I) salts. Copper probably complexes to the zirconocene, possibly with formation of a short-lived alkylcopper-zirconium complex **7**, which also results in the formation of alkane and copper mirror precipitation. In the presence of enone, complexation of the carbonyl group to zirconium facilitates complexation to Cu(I) and transmetalation of the organic residue to give the copper(III) intermediate **12**. The fact that the presence of enone greatly enhances the dissociation of alkylzirconocenes suggests that this complexation could be the

rate-limiting step for both product formation and decomposition to hydrocarbons. It is, however, not clear if transmetalation precedes or follows the formation of the Cu(III) species or if SET pathways[36] are involved in this process. Finally, reductive elimination provides the zirconium enolate **13** and regenerates Cu(I). This reaction scheme is related to the postulated mechanisms in nickel-catalyzed addition reactions of organozirconocenes and conjugate additions with copper reagents.[12d,36]

Scheme II



Variation of Substrates. The broad scope of the copper-catalyzed addition of in situ prepared alkylzirconocenes to enones is documented in Table II. Both the accelerated procedure with CuBr·SMe_2 complex at 40 °C and the slower CuCN at ambient temperature result in moderate to high overall yields with linear or cyclic alkenes and enones. This reaction is surprisingly insensitive toward steric hindrance on the enone (entries 1, 5, 8, 17, 18 & 23). Functionalization at the alkene moiety such as ether, ester, acetal, and aromatic groups are readily tolerated during hydrozirconation and transmetalation (entries 2, 5, 12, 21, 22 & 23). Treatment of dihydropyran **23** with 2 equiv of zirconocene hydrochloride, followed by addition of cyclohexenone and catalytic Cu(I) led to the hydroxyketone **24** via reductive ring opening of the pyran followed by conjugate addition (entry 4). Interestingly, hexylzirconocene added to the more substituted alkene carbon of trimethylcyclohexenedione **30**, possibly as a consequence of the preferential complexation of the zirconocene to the less hindered carbonyl oxygen prior to transmetalation (entry 8). In the presence of 1 equiv of BF_3-etherate, the yield in the conversion of enedione **30** to **31** increased considerably (entry 9). It should be noted that in the absence of tertiary or quarternary centers that would block the migration of zirconium, hydrozirconation of internal alkenes results in terminal addition products (entry 11).

Very high asymmetric induction could be obtained in the copper-catalyzed conjugate addition of organozirconocenes to chiral *N*-acyl-4-benzyl-2-oxazolidinones (entry 10). Imide **33** was isolated as a single diastereomer according to 500 MHz ^1H NMR analysis.[37] The observed (*S*)-configuration at the β-carbon can be explained by a nucleophilic attack opposite to the benzyl group in a chelated conformation of the acyloxazolidinone.[38]

Table II. In Situ Hydrozirconation and Cu(I)-Catalyzed Conjugate Addition of Alkenes to α,β-unsaturated Ketones.

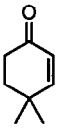
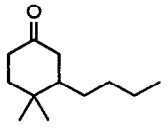
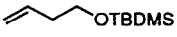
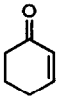
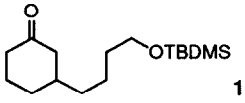
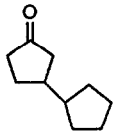
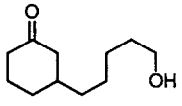
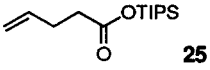
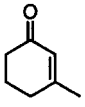
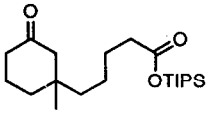
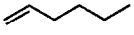
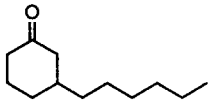
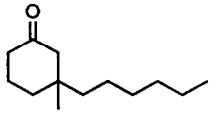
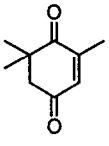
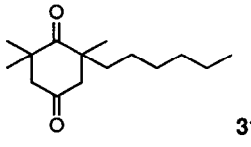
entry	alkene Structure	No.	enone Structure	No.	Cu(I) salt (mol %)	reaction time/Temp.	product Structure	No.	yield (%)[a]
1[b]		**14**		**15**	CuCN (3)	12 h/22 °C		**16**	73
2[c]		**17**		**18**	$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		**19**	76
3[c]		**20**		**21**	$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		**22**	48
4[c,d]		**23**	**18**		$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		**24**	85
5[c]		**25**		**26**	$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		**27**	78
6[c]		**1**	**18**		$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		**28**	79
7[c,e]	**1**		**26**		$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		**29**	69
8[c]	**1**			**30**	$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		**31**	24
9[c,e]	**1**		**30**		$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C	**31**		46

Table II. (Continued).

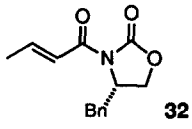
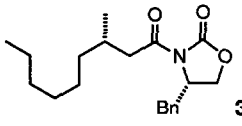
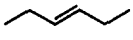
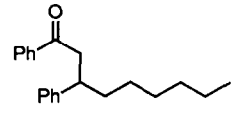
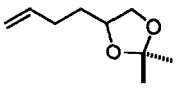
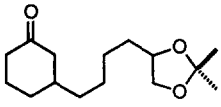
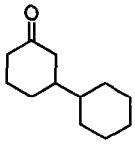
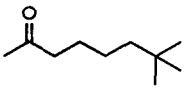
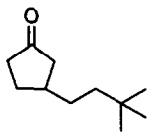
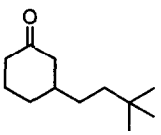
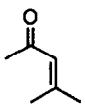
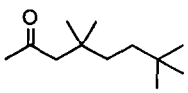
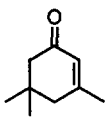
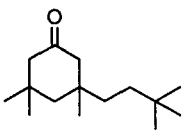
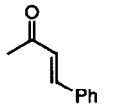
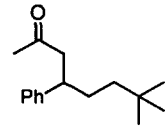
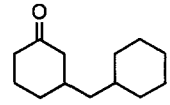
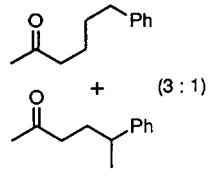
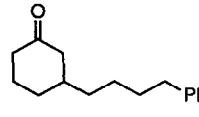
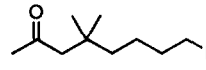
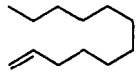
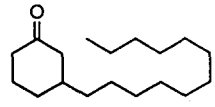
entry	alkene Structure	No.	enone Structure	No.	Cu(I) salt (mol %)	reaction time/Temp.	product Structure	No.	yield (%)[a]
10[c,e]	1			32	$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		33	63
11[c]		34	4		$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		5	51
12[c]		35	18		$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		36	78
13[c]		37	18		$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		38	70
14[b]		39		40	CuCN (3)	16 h/22 °C		41	69
15[b]	39		21		CuCN (3)	8 h/22 °C		42	85
16[b]	39		18		CuCN (3)	4 h/22 °C		43	94
17[b]	39			44	CuCN (3)	48 h/22 °C		45	71
18[b]	39			46	CuCN (3)[f]	47 h/22 °C		47	92

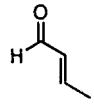
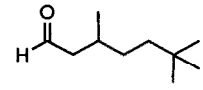
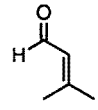
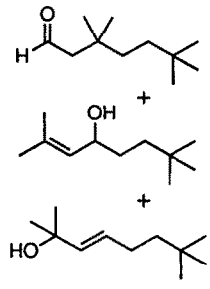
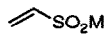
Table II. (Continued).

entry	alkene Structure	No.	enone Structure	No.	Cu(I) salt (mol %)	reaction time/Temp.	product Structure	No.	yield (%)[a]
19[b]	**39**			**48**	CuCN (4)	4 h/22 °C		**49**	81
20[c]		**50**	**18**		$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		**51**	65
21[c]		**52**	**40**		$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		**53a/b**	61
22[b]		**54**	**18**		CuCN (3)	4 h/22 °C		**55**	83
23[b]	**54**		**44**		CuCN (3)	40 h/22 °C		**56**	64
24[c]		**57**	**18**		$CuBr{\cdot}SMe_2$ (10)	10 min/40 °C		**58**	67

[a]Yields are based on enone and refer to chromatographically purified material. [b]Reaction was performed in Et_2O in the presence of 1.25 equiv of the preformed alkylzirconocene reagent. [c]Reaction was performed in THF with 1.1 equiv of the in situ prepared alkylzirconocene reagent. [d]Dihydropyran was reacted with two equiv of zirconocene hydrochloride. [e]One equiv of $BF_3{\cdot}OEt_2$ was used. [f]After 4 h and 8 h, additional 3 mol% of CuCN was added.

Treatment of α,β-unsaturated aldehydes with alkylzirconocenes and copper salts provided only modest yields of the desired addition products (Table III). Concomitant attack at the carbonyl group of the resulting aldehyde was a serious side reaction (entry 2). Vinyl sulfones, however, reacted readily under standard conditions (entry 3).

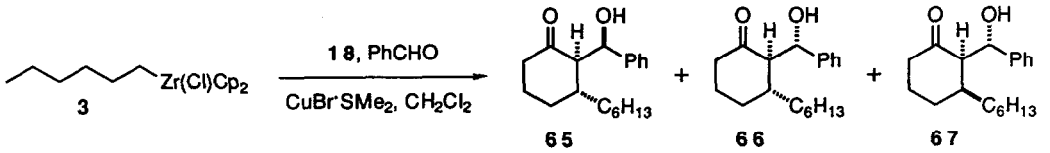
Table III. In Situ Hydrozirconation and Cu(I)-Catalyzed Conjugate Addition of Alkenes to α,β-unsaturated Aldehydes and Sulfones.

entry	alkene No.	enal/sulfone Structure	No.	Cu(I) salt (mol %)	reaction time/Temp.	product Structure	No.	yield (%)[a]
1[b]	**39**		**59**	CuCN (3)	4 h/22 °C		**60**	22
2[b]	**39**		**61**	CuCN (3)	6 h/22 °C	 (3 : 2 :1)	**62a,b,c**	59
3[c,d]	**1**		**63**	CuBr·SMe$_2$ (10)	10 min/40 °C		**64**	51

[a]Yields are based on enal or sulfone and refer to chromatographically purified material. [b]Reaction was performed in Et_2O in the presence of 1.25 equiv of the preformed alkylzirconocene reagent. [c]Reaction was performed in THF with 1.1 equiv of the in situ prepared alkylzirconocene reagent. [d]One equiv of BF_3·OEt_2 was used.

Tandem Conjugate Addition - Enolate Trapping. The zirconium enolates that are formed upon 1,4-addition of alkylzirconocenes to enones should be useful for subsequent aldol reactions.[39,40] Such a tandem conjugate addition-enolate trapping sequence[41] is shown in Scheme III. Copper-catalyzed reaction of hexylzirconocene **3** with cyclohexenone (**18**) in the presence of 1.5 equiv of benzaldehyde at 22 °C gave *syn* aldol **65** as the major product besides *anti* aldols **66** and **67** in 66% yield. Additionally, 15% of 1,4-addition product **28** was isolated. The overall *syn* selectivity in the addition of the intermediate zirconium enolate to benzaldehyde is 3 : 1, which is in good accordance with observations of Yamamoto and Maruyama[42] as well as Panek[43] on zirconium-mediated aldol reactions. Interestingly, however, if this reaction was performed sequentially, e.g. the copper-catalyzed conjugate addition was preformed at 22 °C for 1 h, followed by addition of aldehyde at -78 °C and stirring for 2 h, the selectivity changed in clear favor of the *anti* addition product. A 1: 3 ratio of **65** : **66** was isolated in 46% yield besides 30% of 1,4-addition product **28**. This dependence of *syn* : *anti* selectivities on the reaction temperature is quite possibly due to the involvement of both cyclic and acyclic transition states.[39]

Scheme III

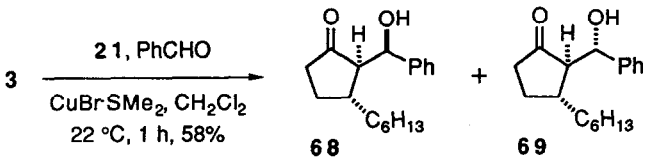


22 °C, 1 h; 66% **65** : **66** : **67** = 9 : 2 : 1

1. **18**, Cu(I), 22 °C, 1 h;
2. PhCHO, -78 °C, 2 h; 46% **65** : **66** : **67** = 1 : 3 : 0

Similarly to cyclohexenone, cyclopentenone (**21**) readily underwent tandem conjugate addition - enolate trapping with benzaldehyde and alkylzirconocene (Scheme IV). In the presence of 10% $CuBr{\cdot}SMe_2$, aldols **68** and **69** were isolated in 58% yield besides 11% of 1,4-addition product. The *syn/anti* ratio was found to be 2 : 1 at room temperature.

Scheme IV



(2 : 1)

Conclusions

The copper-catalyzed conjugate addition of alkylzirconocenes to α,β-unsaturated carbonyl groups is a versatile new synthetic procedure for the selective formation of C,C-bonds. Unlike many traditional copper-mediated processes,[44] sterically hindered substrates react readily, and, due to the shielded and highly covalent character of Zr-C and Cu-C bonds, a broad variety of functional groups is tolerated. Since alkylzirconocenes are prepared in situ by hydrozirconation of alkenes, this procedure represents an overall hydroalkylation of double bonds and complements the previously developed transmetalations of alkenylzirconocenes and alkenylalanes.[13,15]

Experimental Section

General. Anhydrous solvents were freshly distilled from either sodium benzophenone ketyl, P_2O_5, or CaH_2. HMPA was distilled from CaH_2 and stored under argon. $CuBr{\cdot}SMe_2$ was commercially available and used without further purification. TMSCl was distilled from CaH_2 under N_2. All reactions were performed in oven-dried glassware under an argon or nitrogen atmosphere.

General Procedure A for Comparison of Copper-Complexes in Conjugate Additions: 1,3-Diphenylnonan-1-one (5). A solution of 50 mg (0.59 mmol) of 1-hexene in 2.5 mL of THF was treated at 22 °C with 167 mg (0.65 mmol, 1.1 equiv) of $Cp_2Zr(H)Cl$ and stirred at 40 °C for 10 min. After cooling to 22 °C, 123 mg (0.59 mmol) of chalcone and 12 mg (0.06 mmol, 0.1 equiv) of $CuBr{\cdot}SMe_2$ were added. The reaction mixture was stirred at 40 °C for 10 min, quenched with 12 mL of wet Et_2O and extracted with sat. aqueous $NaHCO_3$ (2x). The organic layer was filtered over SiO_2, and concentrated *in vacuo*. The yield of **5** was determined to be 37% by GC analysis (Econo-Cap SE-54, 0.54 mm ID, 30 m / 1.2 μ) with benzophenone as internal standard. Spectral data for chromatographically purified **5**: IR (neat) 3100, 3070, 2998, 2957, 2950, 2938, 2898, 1708, 1695, 1612, 1595, 1509, 1480, 1465, 1392, 1380, 1300, 1284, 1225, 1197, 1020, 1000, 779, 769, 760, 715, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.0-7.9 (m, 2 H), 7.6-7.5 (m, 1 H), 7.5-7.4 (m, 2 H), 7.35-7.2 (m, 5 H), 3.45-3.25 (m, 3 H), 1.8-1.65 (m,2 H), 1.3-1.25 (m, 8 H), 0.88 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 199.0, 137.2, 132.8, 128.4, 128.3, 127.9, 127.5, 126.2, 45.9, 41.2, 36.3, 31.5, 29.2, 27.4, 22.5, 14.0; MS (EI) *m/z* (relative intensity) 294 (M^+, 4), 209 (70), 174 (90), 117 (20), 105 (100), 91 (40), 77 (40); HRMS (EI) *m/z* calcd for $C_{21}H_{26}O$: 294.1984, found: 294.1984.

NMR Data for *n*-Hexylzirconocene 3: ^1H NMR ($CDCl_3$) δ 6.22 (s, 10 H), 1.6-1.5 (m, 2 H), 1.4-1.15 (m, 6 H), 1.1-1.0 (m, 2 H), 0.89 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 112.4, 56.9, 35.6, 34.0, 31.4, 22.7, 14.2.

General Procedure B for Conjugate Additions with Catalytic CuCN: 3-Butyl-4,4-dimethylcyclohexan-1-one (16). A suspension of 21.1 g (72.2 mmol) of $Cp_2Zr(H)Cl$ in 30 mL of toluene was treated with 4.05 g (77.8 mmol) of 1-butene, stirred for 12 h at room temperature, and filtered. The mother liquid was concentrated under reduced pressure, and the residue was dissolved in 30 mL of CH_2Cl_2, diluted with 50 mL of hexane, and filtered. Crystallization at -78 °C gave pure $Cp_2Zr(Cl)C_4H_9$ in 70-85% yield: ^1H NMR (CD_2Cl_2) δ 6.22 (s, 10 H), 1.7-0.8 (m, 9 H); ^{13}C NMR (CD_2Cl_2) δ 113.0, 56.4, 36.7, 29.3, 13.9.

A solution of 1.18 g (3.75 mmol) of $Cp_2Zr(Cl)C_4H_9$ and 372 μL (3.00 mmol) of 4,4-dimethylcyclohexenone (**15**) in 8 mL of Et_2O was treated with 8 mg (0.09 mmol, 3 mol %) of CuCN, stirred for 12 h at 22 °C, and hydrolyzed with 4 mL of saturated aqueous NH_4Cl. After addition of 10 mL of hexane, the reaction mixture was stirred for 2 h, the organic layer was separated, and the aqeous layer was extracted with 10 mL of hexane (3x). The combined organic layers were dried ($MgSO_4$), and the crude **16** was dissolved in EtOH and added at 0 °C to a slight excess of 2,4-dinitrophenylhydrazine in 2 N HCl. After stirring for 1 h, the solid precipitate was filtered off, washed with 2 N HCl and H_2O, and dried *in vacuo* to give 790 mg (73%) of the 2,4-dinitrophenylhydrazone of **16**:[45] ^1H NMR ($CDCl_3$) δ 11.13 (bs, 1 H), 9.05 (d, 1 H, J = 2.5 Hz), 8.26 (dd, 1 H, J = 9.7, 2,5 Hz), 7.95 (d, 1 H, J = 9.7 Hz), 2.7-2.6 (m, 2 H), 2.28 (m, 1 H), 2.11 (m, 1 H), 1.8-0.9 (m, 16 H), 1.01, 0.96 (2s, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.7, 145.6, 137.7, 130.1, 129.1, 123.8, 116.5, 46.9, 39.8, 36.6, 33.5, 30.3, 30.0, 29.1, 23.9, 23.1, 19.7, 14.3.

General Procedure C for Conjugate Additions with Catalytic $CuBr{\cdot}SMe_2$: 3-[4'-Dimethyl-(t-butyl)silyloxy]butylcyclohexan-1-one (19). A solution of 200 mg (1.07 mmol) of 1-dimethyl-(t-butyl)silyloxybut-3-ene (**17**) in 2.5 mL of THF was treated at room temperature with 320 mg (1.24 mmol, 1.1 eq.) of $Cp_2Zr(H)Cl$ and stirred at 40 °C for 10 min. After cooling to room temperature, 103 mg (1.07 mmol) of 2-cyclohexenone (**18**) and 22 mg (0.11 mmol, 0.10 equiv) of copper(I) bromide-dimethyl sulfide complex were added. The reaction mixture was stirred at 40 °C for 10 min, quenched with 25 mL of wet Et_2O and extracted with saturated aqueous $NaHCO_3$ (2x). The organic layer was dried (Na_2SO_4), filtered through SiO_2, and concentrated. The residue was purified by

chromatography on SiO_2 (EtOAc/hexanes, 1:9) to afford 231 mg (76%) of **19** as a colorless oil: IR (neat) 2975, 2960, 2937, 2876, 1722, 1470, 1460, 1400, 1370, 1264, 1235, 1109, 1062, 1017, 843, 820, 784 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.54 (t, 2 H, J = 6.3 Hz), 2.4-2.15 (m, 3 H), 2.0-1.5 (m, 5 H), 1.5-1.4 (m, 2 H), 1.35-1.25 (m, 5 H), 0.83 (s, 9 H), -0.01 (s, 6 H); ^{13}C NMR δ 211.7, 62.8, 48.1, 41.4, 38.9, 36.2, 32.7, 31.1, 25.8, 25.2, 22.8, 18.2, -5.4; MS (EI) *m/z* (relative intensity) 269 (3), 227 (90), 171 (10), 145 (10), 135 (25), 115 (10), 107 (15), 93 (30), 79 (30), 75 (100), 67 (40); HRMS (EI) *m/z* calcd for $C_{16}H_{33}O_2Si$ (M+H): 285.2249, found: 285.2249.

3-Cyclopentylcyclopentan-1-one (22). According to the general procedure C, 200 mg (2.93 mmol) of cyclopentene (**20**), 756 mg (2.93 mmol) of $Cp_2Zr(H)Cl$, 241 mg (2.93 mmol) of 2-cyclopentenone (**21**) and 50 mg (0.24 mmol) of copper(I) bromide-dimethyl sulfide complex afforded **22** in 48% yield as a colorless oil: IR (neat) 3500, 2980, 2962, 2940, 2900, 1751, 1475, 1462, 1418, 1169 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.5-0.8 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ 220.0, 45.8, 44.5, 42.9, 38.6, 31.4, 28.6, 25.0, 22.5, 14.0; MS (EI) *m/z* (relative intensity) 152 (2), 109 (5); HRMS (EI) *m/z* calcd for $C_{10}H_{16}O$: 152.1201, found: 152.1201.

3-(5'-Hydroxy)pentylcyclohexan-1-one (24). According to the general procedure C, 200 mg (2.38 mmol) of 3,4-dihydro-2*H*-pyran (**23**), 1.30 g (5.04 mmol) of $Cp_2Zr(H)Cl$, 228 mg (2.38 mmol) of **18** and 49 mg (0.24 mmol) of copper(I) bromide-dimethyl sulfide complex afforded **24** in 85% yield as a colorless oil: IR (neat) 3490, 2962, 2890, 1749, 1720, 1475, 1460, 1435, 1384, 1370, 1360, 1325, 1310, 1256, 1258 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.54 (t, 2 H, J = 6.6 Hz), 2.45-2.15 (m, 5 H), 2.0-1.4 (m, 7 H), 1.3-1.2 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 212.4, 62.4, 48.0, 42.3, 38.9, 36.3, 32.4, 31.1, 26.3, 25.6, 25.1; MS (EI) *m/z* (relative intensity) 166 ($[M-H_2O]^+$, 5), 141 (5), 123 (5), 97 (100); HRMS (EI) *m/z* calcd for $C_{11}H_{18}O$ ($M-H_2O$): 166.1358, found: 166.1358.

3-(4-[Triisopropylsilyl]oxycarbonyl)butyl-3-methylcyclohexan-1-one (27). According to the general procedure C, 150 mg (0.59 mmol) of ester **25**, 166 mg (0.64 mmol) of $Cp_2Zr(H)Cl$, 65 mg (0.59 mmol) of 3-methyl-2-cyclohexen-1-one (**26**) and 12 mg (0.06 mmol) of copper(I) bromide-dimethyl sulfide complex afforded 170 mg (78%) of **27** as a colorless oil: IR (neat) 2945, 2868, 1716, 1466, 1381, 1255, 1184, 1001, 883 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (t, 2 H, J = 7.3 Hz), 2.22 (t, 2 H, J = 6.5 Hz), 2.11, 2.05 (AB, 2 H, J = 13.4 Hz), 1.80 (h, 2 H, J = 6.3 Hz), 1.60-1.45 (m, 4 H), 1.30-1.15 (m, 7 H), 1.01 (d, 18 H, J = 7.3 Hz), 0.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 212.3, 173.7, 53.8, 41.3, 41.0, 38.5, 35.8, 35.7, 25.8, 25.0, 22.9, 22.1, 17.8, 11.8; MS (EI) *m/z* (relative intensity) 325 ($[M-C_3H_7]^+$, 100), 307 (40), 255 (60), 185 (20), 131 (50), 103 (40), 75 (60), 61 (40); HRMS (EI) *m/z* calcd. for $C_{18}H_{33}O_3Si$ ($M-C_3H_7$): 325.2199, found: 325.2199.

3-Hexylcyclohexan-1-one (28). According to the general procedure C, 200 mg (2.38 mmol) of 1-hexene (**1**), 674 mg (2.61 mmol) of $Cp_2Zr(H)Cl$, 228 mg (2.38 mmol) of **18** and 50 mg (0.24 mmol) of copper(I) bromide-dimethyl sulfide complex afforded 344 mg (79%) of **28** as a colorless oil: IR (neat) 2975, 2945, 2875, 1717, 1465, 1452, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.4-2.2 (m, 3 H), 2.5-1.85 (m, 3 H), 1.8-1.55 (m, 2 H), 1.3-1.2 (m, 11 H), 0.85 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 212.2, 48.2, 41.5, 39.1, 36.6, 31.7, 31.3, 29.3, 26.6, 25.3, 22.6, 14.0; MS (EI) *m/z* (relative intensity) 182 (M^+, 6), 139 (7), 97 (100), 74 (25), 69 (20), 59 (40), 55 (30); HRMS (EI) *m/z* calcd for $C_{12}H_{22}O$: 182.1671, found: 182.1671.

General Procedure D for Conjugate Additions with Catalytic CuBr·SMe_2 in the Presence of BF_3-Etherate: 3-Hexyl-3-methylcyclohexan-1-one (29). A solution of 100 mg (1.19 mmol) of **1** in 5 mL of THF was treated at 22 °C with 337 mg (1.31 mmol, 1.1 equiv) of $Cp_2Zr(H)Cl$ and stirred at 40 °C for 10 min. After cooling to 22 °C, 131 mg (1.19 mmol) of enone **26**, 169 mg (1.19 mmol) of BF_3·OEt_2 and 25 mg (0.12 mmol, 0.10 equiv) of copper(I) bromide-dimethyl sulfide complex were

added. The reaction mixture was stirred at 40 °C for 20 min, quenched with 25 mL of wet Et_2O *and* extracted with sat. aqueous $NaHCO_3$ (2x). The organic layer was dried (Na_2SO_4), filtered over SiO_2, and concentrated in vacuo. The oily residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:9) to give 161 mg (69%) of **29** as a colorless oil: IR (neat) 2930, 2856, 1713, 1462, 1425, 1226 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (t, 2 H, J = 6.6 Hz), 2.17, 2.10 (AB, 2 H, J = 13.4 Hz), 1.85 (h, 2 H, J = 6.2 Hz), 1.70-1.45 (m, 2 H), 1.3-1.2 (m, 10 H), 0.90 (s, 3 H), 0.87 (t, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 212.3, 53.7, 41.5, 41.0, 38.5, 35.7, 31.7, 29.9, 25.0, 23.2, 22.6, 22.1, 14.0; MS (EI) *m/z* (relative intensity) 196 (M^+, 5), 181 (15), 138 (10), 111 (100), 83 (60), 69 (70), 55 (100); HRMS (EI) *m/z* calcd. for $C_{13}H_{24}O$: 196.1827, found: 196.1804.

2-Hexyl-2,6,6-trimethylcyclohexane-1,4-dione (31). According to the general procedure D, 100 mg (1.19 mmol) of **1**, 337 mg (1.31 mmol) of $Cp_2Zr(H)Cl$, 181 mg (1.19 mmol) of 2,6,6-trimethyl-2-cyclohexene-1,4-dione (**30**), 169 mg (1.19 mmol) of $BF_3{\cdot}OEt_2$ and 25 mg (0.12 mmol) of copper(I) bromide-dimethyl sulfide complex afforded 131 mg (46%) of **31** as a colorless oil: IR (neat) 2959, 2932, 2858, 1707, 1468, 1244, 1172, 1132 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.71, 2.42 (AB, 2 H, J = 18.0 Hz), 2.53 (s, 2 H), 1.65-1.55 (m, 1 H), 1.3-1.0 (m, 9 H), 1.11 (s, 3 H), 1.09 (s, 3 H), 1.06 (s, 3 H), 0.78 (t, 3 H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 215.9, 208.8, 50.4, 48.2, 46.9, 43.3, 39.0, 31.5, 29.6, 26.8, 26.2, 25.6, 24.3, 22.5, 14.0; MS (EI) *m/z* (relative intensity) 238 (M^+, 2), 223 (16), 195 (8), 154 (50), 83 (30), 69 (70), 56 (100); HRMS (EI) *m/z* calcd. for $C_{15}H_{26}O_2$: 238.1933, found: 238.1927.

[3(3*S*),4*S*]-(3-Methyl-1-oxononyl)-4-phenylmethyl-2-oxazolidinone (33). According to the general procedure D, 17 mg (0.20 mmol) of **1**, 57 mg (0.22 mmol) of $Cp_2Zr(H)Cl$, 50 mg (0.20 mmol) of oxazolidinone **32**,[46] 28 mg (0.20 mmol) of $BF_3{\cdot}OEt_2$ and 4 mg (0.02 mmol) of copper(I) bromide-dimethyl sulfide complex afforded 42 mg (63%) of **33** as a white solid: IR (neat) 2957, 2926, 2856, 1784, 1699, 1454, 1387, 1352, 1209, 1099, 762, 746, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35-7.20 (m, 5 H), 4.71-4.63 (m, 1 H), 4.21-4.12 (m, 2 H), 3.30 (dd, 1 H, J = 13.3, 3.2 Hz), 2.97 (dd, 1 H, J = 16.3, 5.5 Hz), 2.77-2.66 (m, 2 H), 2.2-2.0 (m, 1 H), 1.5-1.2 (m, 10 H), 0.96 (d, 3 H, J = 6.7 Hz), 0.85 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 172.9, 153.5, 135.4, 129.5, 129.0, 127.4, 66.1, 55.2, 42.6, 38.0, 36.9, 31.9, 29.6, 29.5, 27.0, 22.7, 19.8, 14.2; MS (EI) *m/z* (relative intensity) 331 (M^+, 4), 240 (10), 219 (10), 155 (100), 134 (10), 117 (10), 91 (10), 71 (30), 57 (30); HRMS (EI) *m/z* calcd. for $C_{20}H_{29}NO_3$: 331.2147, found: 331.2144.

1,3-Diphenylnonan-1-one (5). According to the general procedure C, 200 mg (2.38 mmol) of (*E*)-3-hexene (**34**), 675 mg (2.62 mmol) of $Cp_2Zr(H)Cl$, 495 mg (2.38 mmol) of chalcone (**4**) and 49 mg (0.24 mmol) of copper(I) bromide-dimethyl sulfide complex afforded **5** in 51% yield as a colorless oil.

3-[5',6'-(Dimethylmethylenedioxy)hexyl]cyclohexan-1-one (36). According to the general procedure C, 100 mg (0.64 mmol) of 1,2-(dimethylmethylenedioxy)hex-5-ene (**35**), 180 mg (0.70 mmol) of $Cp_2Zr(H)Cl$, 61 mg (0.64 mmol) of 2-cyclohexenone (**18**), and 13 mg (0.06 mmol) of copper(I) bromide-dimethyl sulfide complex afforded **36** in 78% yield as a colorless oil: IR (neat) 3025, 2975, 2900, 1720, 1460, 1430, 1380, 1375, 1325, 1260, 1230, 1165, 865, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0-3.9 (m, 2 H), 3.45-3.35 (m, 1 H), 2.35-2.15 (m, 3 H), 2.0-1.3 (m, 12 H), 1.34, 1.29 (2s, 6 H); ^{13}C NMR ($CDCl_3$) δ 211.8, 108.5, 75.9, 69.3, 48.0, 41.4, 38.8, 36.3, 33.4, 31.2, 26.8, 26.6, 25.7, 25.6, 25.1; MS (EI) *m/z* (relative intensity) 239 ($[M-CH_3]^+$, 100), 197 (30), 179 (30), 161 (30), 135 (25), 121 (20), 97 (50), 81 (81), 72 (80), 69 (30), 55 (30); HRMS (EI) *m/z* calcd for $C_{14}H_{23}O_3$ ($M-CH_3$): 239.1647, found: 239.1647.

3-Cyclohexylcyclohexan-1-one (38). According to the general procedure C, 200 mg (2.43 mmol) of cyclohexene (**37**), 640 mg (2.48 mmol) of $Cp_2Zr(H)Cl$, 233 mg (2.43 mmol) of **18**, and 50

mg (0.24 mmol) of copper(I) bromide-dimethyl sulfide complex afforded **38** in 70% yield as a colorless oil: IR (neat) 3500, 2960, 2880, 1735, 1720, 1460, 1436, 1359, 1329, 1278, 1240, 1235, 900, 875, 760, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8-2.3 (m, 20 H); ^{13}C NMR δ ($CDCl_3$) 212.1, 45.3, 44.4, 42.4, 41.3, 29.7, 29.6, 28.2, 26.3, 25.4; MS (EI) *m/z* (relative intensity) 180 (M^+, 3), 137 (10), 122 (16), 97 (100), 69 (15), 55 (30); HRMS (EI) *m/z* calcd for $C_{12}H_{20}O$: 180.1514, found: 180.1514.

7,7-Dimethyl-2-octanone (41). According to the general procedure B, 1.28 g (3.75 mmol) of $Cp_2Zr(Cl)CH_2CH_2C(CH_3)_3$, 244 μL 3.00 mmol) of methyl vinyl ketone (**40**), and 8 mg (0.09 mmol) of CuCN afforded 322 mg (2.06 mmol, 69%) of **41** as a slightly yellowish oil:[45] ^1H NMR ($CDCl_3$) δ 2.41 (m, 2 H), 2.11 (t, 3 H, J = 0.6 Hz), 1.51 (m, 2 H), 1.3-1.1 (m, 4 H), 0.83 (s, 9 H); ^{13}C NMR δ ($CDCl_3$) 209.5, 44.1, 44.0, 30.4, 30.0, 29.5, 24.9, 24.4.

3-(3,3-Dimethylbutyl)cyclopentanone (42). According to the general procedure B, 1.28 g (3.75 mmol) of $Cp_2Zr(Cl)CH_2CH_2C(CH_3)_3$, 244 μL (3.00 mmol) of cyclopentenone (**21**), and 8 mg (0.09 mmol) of CuCN afforded 430 mg (2.56 mmol, 85%) of **42** as a slightly yellowish oil:[45] ^1H NMR ($CDCl_3$) δ 2.35-1.9 (m, 5 H), 1.68 (ddd, 1 H, J = 18, 10, 1 Hz), 1.5-1.0 (m, 5 H), 0.79 (s, 9 H); ^{13}C NMR δ ($CDCl_3$) 219.8, 45.4, 42.2, 38.5, 37.9, 30.6, 30.1, 29.6, 29.3.

3-(3,3-Dimethylbutyl)cyclohexanone (43). According to the general procedure B, 1.28 g (3.75 mmol) of $Cp_2Zr(Cl)CH_2CH_2C(CH_3)_3$, 300 μL (3.00 mmol) of cyclohexenone (**18**), and 8 mg (0.09 mmol) of CuCN afforded 513 mg (2.81 mmol, 94%) of **43** as a slightly yellowish oil:[45] ^1H NMR ($CDCl_3$) δ 2.5-2.15 (m, 4 H), 2.1-1.8 (m, 2 H), 1.7-1.5 (m, 2 H), 1.4-1.1 (m, 5 H), 0.82 (s, 9 H); ^{13}C NMR δ ($CDCl_3$) 212.1, 48.4, 41.6, 41.2, 40.0, 31.5, 30.2, , 29.4, 25.4.

4,4,7,7-Tetramethyl-2-octanone (45). According to the general procedure B, 1.28 g (3.75 mmol) of $Cp_2Zr(Cl)CH_2CH_2C(CH_3)_3$, 340 μL (3.00 mmol) of 4-methylpentenone **44**, and 8 mg (0.09 mmol) of CuCN afforded 393 mg (2.13 mmol, 71%) of **45** as a slightly yellowish oil:[45] ^1H NMR ($CDCl_3$) δ 2.29 (s, 2 H), 2.10 (s, 3 H), 1.3-1.05 (m, 4 H), 0.95 (s, 6 H), 0.83 (s, 9 H); ^{13}C NMR δ ($CDCl_3$) 209.2, 54.0, 38.0, 36.9, 33.4, 32.7, 30.2, 29.5, 27.5.

3-(3,3-Dimethylbutyl)-3,5,5-trimethylcyclohexanone (47). According to the general procedure B, 1.28 g (3.75 mmol) of $Cp_2Zr(Cl)CH_2CH_2C(CH_3)_3$, 449 μL (3.00 mmol) of isopherone (**46**), and a total of 3x8 mg (0.27 mmol) of CuCN afforded 92% of **47** as a colorless oil:[45] ^1H NMR ($CDCl_3$) δ 2.2-2.0 (m, 4 H), 1.65-1.45 (m, 2 H), 1.4-0.95 (m, 4 H), 1.02, 1.00, 0.95 (3s, 9 H), 0.83 (s, 9 H); ^{13}C NMR δ ($CDCl_3$) 212.6, 54.5, 53.5, 39.4, 38.6, 37.6, 36.2, 32.4, 30.8, 30.2, 29.5, 27.6.

3-(3,3-Dimethylbutyl)-3,5,5-trimethylcyclohexanone (49). According to the general procedure B, 1.28 g (3.75 mmol) of $Cp_2Zr(Cl)CH_2CH_2C(CH_3)_3$, 440 mg (3.00 mmol) of 4-phenylbutenone **48**, and 10 mg (0.11 mmol) of CuCN afforded 563 mg (2.43 mmol, 81%) of **49** as a yellowish oil:[45] ^1H NMR ($CDCl_3$) δ 7.35-7.1 (m, 5 H), 3.15-3.0 (m, 1 H), 2.73 (d, 2 H, J = 7 Hz), 2.01 (s, 3 H), 1.7-1.5 (m, 2 H), 1.3-0.9 (m, 2 H), 0.82 (s, 9 H); ^{13}C NMR δ ($CDCl_3$) 208.2, 145.0, 128.7, 127.7, 126.6, 51.3, 42.3, 41.9, 31.5, 30.9, 30.4, 29.5.

3-[Cyclohexylmethyl]cyclohexan-1-one (51). According to the general procedure C, 200 mg (2.08 mmol) of methylenecyclohexane (**50**), 590 mg (2.29 mmol) of $Cp_2Zr(H)Cl$, 200 mg (2.08 mmol) of 2-cyclohexenone (**18**), and 43 mg (0.21 mmol) of copper(I) bromide-dimethyl sulfide complex afforded **51** in 66% yield as a colorless oil: IR (neat) 2950, 2875, 1720, 1460, 1435, 1360, 1325, 1235 cm^{-1}; ^1H NMR δ 2.35-2.1 (m, 3 H), 1.9-1.75 (m, 4 H), 1.65-1.5 (m, 6 H), 1.3-1.0 (m, 7 H), 0.8-0.65 (m, 2 H); ^{13}C NMR δ 211.7, 48.1, 44.3, 41.3, 35.6, 34.0, 33.2, 33.1, 31.4, 26.3, 26.0, 25.1; MS (EI) *m/z* (relative intensity) 194 (M^+, 3), 151 (10), 97 (100), 55 (25); HRMS (EI) *m/z* calcd for $C_{13}H_{22}O$: 194.1671, found: 194.1671.

6-Phenylhexan-2-one (53a) and 5-phenylhexan-2-one (53b). According to the general procedure C, 250 mg (2.40 mmol) of styrene (**52**), 640 mg (2.48 mmol) of $Cp_2Zr(H)Cl$, 168 mg (2.40 mmol) of methyl vinyl ketone (**40**) and 49 mg (0.24 mmol) of copper(I) bromide-dimethyl sulfide complex afforded a 3 : 1 mixture of **53a** and **53b** in 61% yield as a colorless oil: IR (neat) 3100, 3062, 2190, 1735, 1722, 1700, 1620, 1510, 1464, 1449, 1422, 1371, 1291, 1250, 1220, 1200, 1180, 1119, 1081, 1049, 1023, 1010, 945, 923, 900, 875, 700, 790, 770, 729 cm^{-1}; MS (EI) *m/z* (relative intensity) 176 (M^+, 40), 158 (10), 129 (15), 118 (85), 105 (20), 91 (75), 71 (40), 58 (20); HRMS (EI) *m/z* calcd for $C_{12}H_{16}O$: 176.1201, found: 176.1201.

Major isomer: ^1H NMR δ 7.35-7.1 (m, 5 H), 2.7-2.6 (m, 2 H), 2.5-2.4 (m, 2 H), 2.13 (s, 3 H), 1.7-1.6 (m, 4 H); ^{13}C NMR δ 208.8, 142.0, 128.2, 128.1, 125.6, 43.4, 35.6, 30.8, 29.7, 23.3.

Minor isomer: ^1H NMR δ 7.35-7.1 (m, 5 H), 2.75-2.6 (m, 1 H), 2.35-2.5 (m, 2 H), 2.06 (s, 3 H), 1.95-1.75 (m, 2 H), 1.28 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 209.8, 146.3, 128.3, 126.9, 126.0, 125.6, 41.7, 39.2, 31.7, 29.7, 22.3.

3-(4-Phenylbutyl)cyclohexanone (55). According to the general procedure B, 1.46 g (3.75 mmol) of $Cp_2Zr(Cl)(CH_2)_4Ph$, 300 μL (3.00 mmol) of cyclohexenone (**18**), and 8 mg (0.09 mmol) of CuCN afforded 570 mg (2.49 mmol, 83%) of **55** as a yellowish oil:[45] ^1H NMR ($CDCl_3$) δ 7.35-7.15 (m, 5 H), 2.63 (m, 2 H), 2.5-2.2 (m, 3 H), 2.15-1.5 (m, 7 H), 1.45-1.25 (m, 5 H); ^{13}C NMR δ ($CDCl_3$) 211.9, 142.6, 128.5, 128.4, 125.8, 48.2, 41.5, 39.1, 36.5, 35.9, 31.6, 31.3, 26.3, 25.3.

3,4-Dimethyl-8-phenyl-2-octanone (56). According to the general procedure B, 1.46 g (3.75 mmol) of $Cp_2Zr(Cl)(CH_2)_4Ph$, 340 μL (3.00 mmol) of **44**, and 8 mg (0.09 mmol) of CuCN afforded 446 mg (1.92 mmol, 64%) of **56** as a colorless liquid:[45] ^1H NMR ($CDCl_3$) δ 7.35-7.15 (m, 5 H), 2.65 (m, 2 H), 2.33 (bs, 2 H), 2.12 (t, 3 H, J = 0.5 Hz), 1.7-1.55 (m, 2 H), 1.5-1.3 (m, 4 H), 1.01 (s, 6 H); ^{13}C NMR δ ($CDCl_3$) 208.9, 142.7, 128.4, 128.3, 125.7, 53.8, 35.9, 33.5, 32.5, 32.2, 27.3, 23.8.

3-Dodecylcyclohexan-1-one (58). According to the general procedure C, 200 mg (1.19 mmol) of 1-dodecene (**57**), 337 mg (1.31 mmol) of $Cp_2Zr(H)Cl$, 114 mg (1.19 mmol) of **18** and 24 mg (0.12 mmol) of copper(I) bromide-dimethyl sulfide complex afforded **58** in 67% yield as a colorless oil: IR (neat) 2963, 2875, 1725, 1475, 1239 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.5-2.2 (m, 3 H), 2.05-1.85 (m, 3 H), 1.8-1.55 (m, 2 H), 1.35-1.25 (m, 23 H), 0.87 (t, 3 H, J = 6.9 Hz); ^{13}C NMR δ 212.2, 48.2, 41.5, 39.1, 36.6, 31.9, 31.3, 29.6, 29.3, 26.6, 25.3, 22.7, 14.1; MS (EI) *m/z* (relative intensity) 266 (M^+, 2), 223 (2), 97 (100); HRMS (EI) *m/z* calcd for $C_{18}H_{34}O$: 266.2609, found: 266.2609.

3,6,6-Trimethylheptanal (60). According to the general procedure B, 1.28 g (3.75 mmol) of $Cp_2Zr(Cl)CH_2CH_2C(CH_3)_3$, 248 μL (3.00 mmol) of enal **59**, and 8 mg (0.09 mmol) of CuCN afforded 101 mg (0.65 mmol, 22%) of **60** as a yellowish liquid:[45] ^1H NMR ($CDCl_3$) δ 9.77 (t, 1 H, J = 2.3 Hz), 2.5-2.2 (m, 2 H), 2.1-1.9 (m, 1 H), 1.4-1.1 (m, 4 H), 0.97 (d, 3 H, J = 6.7 Hz), 0.87 (s, 9 H); ^{13}C NMR δ ($CDCl_3$) 203.2, 51.3, 41.5, 31.9, 30.4, 29.5, 29.2, 20.3.

3,3,6,6-Tetramethylheptanal (62a), 2,7,7-trimethyl-2-octen-4-ol (62b) and 2,7,7-trimethyl-3-octen-2-ol (62c). According to the general procedure B, 1.28 g (3.75 mmol) of $Cp_2Zr(Cl)CH_2CH_2C(CH_3)_3$, 290 μL (3.00 mmol) of enal **61**, and 8 mg (0.09 mmol) of CuCN afforded 142 mg (0.83 mmol, 28%) of **62a** and 168 mg (0.93 mmol, 31%) of a 2 : 1 mixture of **62b** and **62c** as yellowish liquids.[45]

62a: ^1H NMR ($CDCl_3$) δ 9.83 (t, 1 H, J = 3.2 Hz), 2.4 (d, 2 H, J = 3.2 Hz), 1.35-1.05 (m, 4 H), 1.03 (s, 6 H), 0.87 (s, 9 H); ^{13}C NMR δ ($CDCl_3$) 203.9, 54.9, 37.9, 37.3, 33.4, 30.2, 29.5, 27.8.

Characteristic peaks for **62b**: ^1H NMR ($CDCl_3$) δ 5.15 (m, 1 H), 4.27 (dt, 1 H, J = 8.8, 6 Hz), 1.72, 1.67 (2d, 3 H, J = 1.2 Hz), 0.87 (s, 9 H); ^{13}C NMR δ ($CDCl_3$) 137.6, 128.6, 69.7, 39.8, 33.1, 30.2, 29.6.

Characteristic peaks for **62c**: ^{1}H NMR ($CDCl_3$) δ 5.6 (m, 2 H), 1.29 (s, 6 H), 0.88 (s, 9 H); ^{13}C NMR δ ($CDCl_3$) 135.3, 128.3, 64.7, 44.0, 30.0, 29.6.

Methyl octyl sulfone (64). According to the general procedure D, 40 mg (0.48 mmol) of **1**, 135 mg (0.52 mmol) of $Cp_2Zr(H)Cl$, 50 mg (0.48 mmol) of methyl vinyl sulfone (**63**), 68 mg (0.48 mmol) of $BF_3{\cdot}OEt_2$ and 10 mg (0.05 mmol) of copper(I) bromide-dimethyl sulfide complex afforded 47 mg (51%) of **64**[47] as a white solid: ^{1}H NMR ($CDCl_3$) δ 3.02-2.97 (m, 2 H), 2.89 (s, 3 H), 1.5-1.2 (m, 12 H), 0.87 (t, 3 H, J = 6.9 Hz).

(2*RS*,2(1*RS*),3*RS*)-3-Hexyl-2-(1-hydroxy-1-phenylmethyl)cyclohexan-1-one (65), (2*RS*,2(1*SR*),3*RS*)-3-hexyl-2-(1-hydroxy-1-phenylmethyl)cyclohexan-1-one (66) and (2*RS*,2(1*SR*),3*SR*)-3-hexyl-2-(1-hydroxy-1-phenylmethyl)cyclohexan-1-one (67). A solution of 100 mg (1.19 mmol) of 1-hexene in 4 mL of CH_2Cl_2 was treated at 22 °C with 336 mg (1.30 mmol, 1.1 equiv) of $Cp_2Zr(H)Cl$ and stirred for 30 min. To the resulting clear solution were added 126 mg (1.19 mmol) of benzaldehyde in 2 mL of CH_2Cl_2, 114 mg (1.19 mmol) of 2-cyclohexen-1-one (**18**) in 2 mL of CH_2Cl_2 and 25 mg (0.12 mmol, 0.10 equiv) of copper(I) bromide-dimethyl sulfide complex. The mixture was stirred at 22 °C for 1 h, quenched with 25 mL of wet Et_2O and extracted with sat. aqueous (2x). The organic layer was dried (Na_2SO_4), filtered over SiO_2, and concentrated *in vacuo*. The oily residue was purified by silica gel chromatography (EtOAc/hexanes, 1:9) to give 32 mg (15%) of **28**, 173 mg (50%) of **65**, 36 mg (11%) of **66** and 19 mg (6%) of **67** as colorless oils. If the reaction mixture was cooled to -78 °C before the addition of benzaldehyde, and subsequently stirred at that temperature for 2 h, a 1 : 3 ratio of **65** : **66** was isolated in 46% yield.

65: IR (neat) 3391, 3063, 3028, 2926, 2855, 1705, 1603, 1493, 1456, 1309, 1244, 1207, 1103, 1039, 754, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33-7.23 (m, 5 H), 4.95 (t, 1 H, J = 7.0 Hz), 3.50 (d, 1 H, J = 7.3 Hz), 2.59 (t, 1 H, J = 7.0 Hz), 2.48-2.42 (m, 1 H), 2.33-2.27 (m, 1 H), 2.00-1.79 (m, 4 H), 1.50-1.16 (m, 11 H), 0.85 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 214.8, 143.1, 128.3, 127.4, 126.1, 72.8, 62.2, 40.8, 39.6, 32.8, 31.6, 29.1, 27.3, 26.2, 24.4, 22.5, 14.0; MS (EI) *m/z* (relative intensity) 270 ([M-H_2O]$^+$, 1), 182 (5), 139 (10), 105 (25), 97 (100), 77 (40), 69 (20), 55 (30); HRMS (EI) *m/z* calcd. for $C_{19}H_{26}O$ (M-H_2O): 270.1984, found: 270.1984.

66: IR (neat) 3424, 3030, 2926, 2856, 1699, 1603, 1495, 1454, 1307, 1236, 1116, 1041, 765, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32-7.23 (m, 5 H), 5.10 (d, 1 H, J = 5.7 Hz), 3.35-3.25 (bs, 1 H), 2.61 (dd, 1 H, J = 6, 7 Hz), 2.36-2.22 (m, 2 H), 2.1-1.8 (m, 3 H), 1.73-1.69 (m, 1 H), 1.50-1.45 (m, 1 H), 1.3-1.1 (m, 10 H), 0.86 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 214.8, 142.1, 128.4, 127.7, 126.5, 73.2, 61.8, 41.6, 37.6, 33.4, 31.8, 29.3, 27.4, 26.4, 23.0, 22.6, 14.1; MS (EI) *m/z* (relative intensity) 270 ([M-H_2O]$^+$, 1), 182 (5), 105 (20), 97 (100), 77 (20), 55 (20); MS (CI) *m/z* 271 ([M+1-H_2O]$^+$).

67: IR (neat) 3451, 3032, 2926, 2856, 1701, 1496, 1458, 1379, 1311, 1211, 1138, 760, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39-7.30 (m, 5 H), 5.05 (dd, 1 H, J = 9.5, 2.5 Hz), 3.40 (d, 1 H, J = 2.5 Hz), 2.87 (dd, 1 H, J = 9.5, 4.3 Hz), 2.43-2.35 (m, 2 H), 1.91-1.66 (m, 4 H), 1.36-1.05 (m, 11 H), 0.83 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 215.3, 140.4, 128.6, 128.1, 127.2, 71.8, 62.5, 42.5, 38.7, 31.6, 29.8, 29.0, 27.4, 26.4, 25.9, 22.6, 22.3, 14.1; MS (EI) *m/z* (relative intensity) 270 ([M-H_2O]$^+$, 3), 182 (5), 105 (20), 97 (100), 77 (25), 55 (20); HRMS (EI) *m/z* calcd. for $C_{12}H_{22}O$ (M-PhCHO): 182.1671, found: 182.1671.

(2*RS*,2(1*RS*),3*RS*)-3-Hexyl-2-(1-hydroxy-1-phenylmethyl)cyclopentan-1-one (68) and (2*RS*,2(1*SR*),3*RS*)-3-hexyl-2-(1-hydroxy-1-phenylmethyl)cyclopentan-1-one (69). A solution of 100 mg (1.19 mmol) of 1-hexene in 4 mL of CH_2Cl_2 was treated at 22 °C with 336 mg (1.30 mmol, 1.1 equiv) of $Cp_2Zr(H)Cl$ and stirred for 30 min. The resulting clear solution was cooled to 0 °C, and 98 mg (1.19 mmol) of 2-cyclopenten-1-one (**21**), 190 mg (1.79 mmol, 1.5 equiv) of benzaldehyde in 2

mL of CH_2Cl_2 and 25 mg (0.12 mmol, 0.10 equiv) of copper(I) bromide-dimethyl sulfide complex were added. The reaction mixture was stirred at 22 °C for 1 h, quenched with 25 mL of wet Et_2O and extracted with sat. aqueous $NaHCO_3$ (2x). The organic layer was dried (Na_2SO_4), filtered over SiO_2, and concentrated *in vacuo*. The oily residue was purified by silica gel chromatography (EtOAc/hexanes, 1:9) to give 22 mg (11%) of 3-hexylcyclopentanone, 128 mg (40%) of **68** and 61 mg (19%) of **69** as colorless oils.

68: IR (neat) 3443, 3063, 3028, 2957, 2926, 2856, 1734, 1603, 1495, 1452, 1404, 1334, 1282, 1157, 1028, 740, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36-7.25 (m, 5 H), 5.18 (dd, 1 H, J = 6.6, 4.1 Hz), 3.34 (d, 1 H, J = 6.6 Hz), 2.33-2.21 (m, 1 H), 2.24 (dd, 1 H, J = 9.8, 4.1 Hz), 2.11-1.98 (m, 3 H), 1.36-1.08 (m, 11 H), 0.86 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 222.3, 142.3, 128.3, 127.4, 125.8, 72.7, 60.6, 39.1, 36.7, 34.8, 31.7, 29.1, 27.2, 26.7, 22.6, 14.1; MS (EI) *m/z* (relative intensity) 256 ([M-H_2O]$^+$, 2), 168 (10), 105 (30), 97 (10), 83 (100), 77 (40), 55 (30); HRMS (EI) *m/z* calcd. for $C_{11}H_{20}O$ (M-PhCHO): 168.1514, found: 168.1514.

69: IR (neat) 3462, 3065, 3032, 2957, 2926, 2856, 1722, 1456, 1406, 1331, 1257, 1203, 1155, 1041, 750, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36-7.26 (m, 5 H), 4.72 (dd, 1 H, J = 8.2, 1.5 Hz), 4.33 (d, 1 H, J = 1.6 Hz), 2.5-2.4 (m, 1 H), 2.3-2.2 (m, 1 H), 2.16-2.09 (m, 1 H), 2.12 (dd, 1 H, J = 9.5, 8.2 Hz), 1.9-1.75 (m, 1 H), 1.45-1.35 (m, 1 H), 1.25-0.7 (m, 10 H), 0.83 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 223.3, 141.3, 128.4, 128.1, 126.8, 75.2, 60.2, 39.1, 38.2, 34.3, 31.5, 28.9, 27.0, 26.4, 22.5, 14.1; MS (EI) *m/z* (relative intensity) 256 ([M-H_2O]$^+$, 2), 168 (10), 105 (30), 97 (10), 83 (100), 55 (30); HRMS (EI) *m/z* calcd. for $C_{11}H_{20}O$ (M-PhCHO): 168.1514, found: 168.1514.

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