Palladium-Catalyzed Intramolecular Hydroalkylation of Alkenyl- β-Keto Esters, α-Aryl Ketones, and Alkyl Ketones in the Presence of Me_3SiCl or HCl

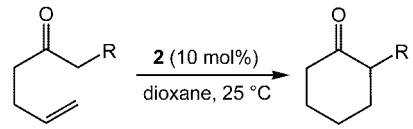
Xiaoqing Han, Xiang Wang, Tao Pei, and Ross A. Widenhoefer*[a]

Abstract: Reaction of 3-butenyl β-keto esters or 3-butenyl α-aryl ketones with a catalytic amount of $[PdCl_2(CH_3CN)_2]$ (**2**) and a stoichiometric amount of Me_3SiCl or $Me_3SiCl/CuCl_2$ in dioxane at 25–70 °C formed 2-substituted cyclohexanones in good yield with high regioselectivity. This protocol tolerated a number of ester and aryl groups and tolerated substitution at the allylic, enolic, and *cis* and *trans* terminal olefinic positions. In situ NMR experiments indicated that the chlorosilane was not directly involved in palladium-catalyzed hydroalkylation, but rather served as a source of HCl, which presumably catalyzes enolization of the ketone. Identification of HCl as the active promoter of palladium-catalyzed hydroalkylation led to the development of an effective protocol for the hydroalkylation of alkyl 3-butenyl ketones that employed sub-stoichiometric amounts of **2**, HCl, and $CuCl_2$ in a sealed tube at 70 °C.

Keywords: C–C coupling · cyclization · enols · homogeneous catalysis · palladium

Introduction

In response to the absence of a general and effective method for the alkylation of unactivated olefins with stabilized carbon nucleophiles, we have recently reported the palladium-catalyzed intramolecular hydroalkylation of 3-butenyl β-diketones to form 2-acylcyclohexanones [Eq. (1)].[1,2] For example, treatment of 7-octene-2,4-dione (**1**) with a catalytic amount of $PdCl_2(CH_3CN)_2$ (**2**; 10 mol%) in dioxane at room temperature for 16 h led to the formation of 2-acetylcyclohexanone (**3**) in 81% yield as a single regioisomer [Eq. (1)].[1]

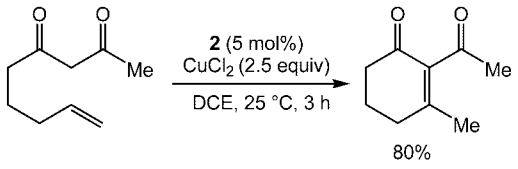


(1)

1 (R = COMe)
4 (R = CO_2Me)

3 (81%)
5 (21%)

Similarly, we have reported the palladium-catalyzed intramolecular oxidative alkylation of 4-pentenyl β-diketones to form 2-acyl-2-cyclohexenones [Eq. (2)].[3,4] As an example, reaction of 8-nonene-2,4-dione with a catalytic amount of **2** (5 mol%) and a stoichiometric amount of $CuCl_2$ in dioxane at room temperature for 3 h led to isolation of 2-acetyl-3-methyl-2-cyclohexenone in 80% yield [Eq. (2)].[3,4]



(2)

80%

On the basis of deuterium-labeling, kinetic, and in situ NMR experiments, we have proposed a mechanism for the palladium-catalyzed hydroalkylation of **1** involving attack of the pendant enol on the palladium-complexed olefin of **I** to form the palladium–cyclohexyl species **II** (Scheme 1).[2,4,5] Isomerization of **II** through iterative β-hydride elimination/addition followed by protonolysis of the palladium–enolate species **III** forms **3** with regeneration of **2** (Scheme 1).

β-Keto esters possess a less acidic C–H bond and a lower $K_{enol/ketone}$ than do β-diketones (Table 1),[6–9] and it is likely for this reason that the palladium-catalyzed hydroalkylation of 3-butenyl β-keto esters was markedly less efficient than was the hydroalkylation of 3-butenyl β-diketones.[1,2] For example, treatment of methyl 3-oxo-6-heptenoate (**4**) with a catalytic amount of **2** at 25 °C for 26 h formed 2-carbome-

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. Experimental procedures and spectroscopic data for alkenyl ketones and X-ray crystallographic data for *trans*-**23**.

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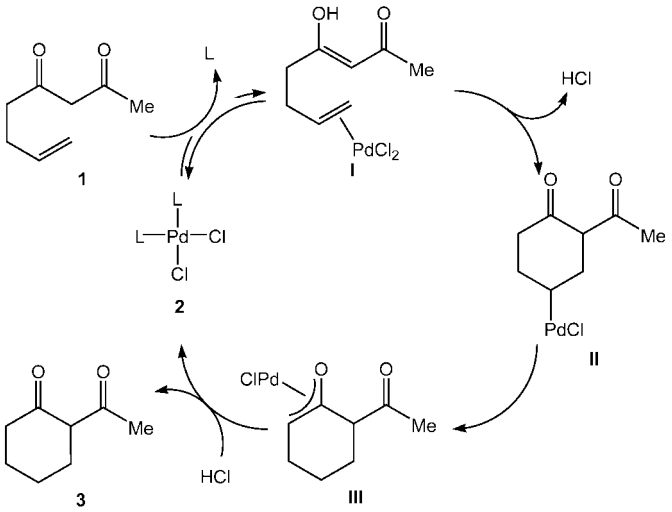
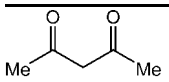
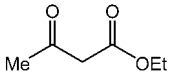
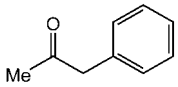
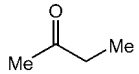
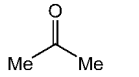


Scheme 1.

Table 1. pK_a and $K_{enol/ketone}$ for carbon nucleophiles.

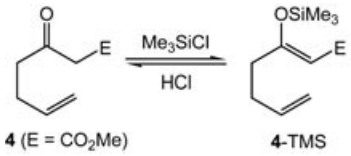
Carbon nucleophile	pK_a (DMSO)[a]	$K_{enol/ketone}$
	13.3	1.3(DMSO)[b] 5.1($CDCl_3$)[b]
	14.2	0.04(DMSO)[b] 0.09($CDCl_3$)[b]
	19.9	7.9×10^{-5}(H_2O)[c]
	24.4	5.0×10^{-9}(H_2O)[d]
	26.5	6.3×10^{-8}(H_2O)[d]

[a] Taken from reference [6]. [b] Taken from reference [7]. [c] Taken from reference [8]. [d] Taken from reference [9].

thoxycyclohexanone (**5**) in only 21% yield [Eq. (1)]. Given the precipitous drop in the reactivity of 3-butenyl β-keto esters relative to 3-butenyl β-diketones toward palladium-catalyzed intramolecular hydroalkylation, it was not surprising that olefins tethered to even less reactive carbon nucleophiles such as α-aryl ketones or dialkyl ketones (Table 1) failed to undergo palladium-catalyzed intramolecular hydroalkylation. We therefore directed our efforts toward expanding the scope of palladium-catalyzed olefin alkylation with respect to the carbon nucleophile. Here we report the development of effective procedures for the palladium-catalyzed hydroalkylation of alkenyl-β-keto esters, α-aryl ketones, and alkyl ketones.[10]

Results and Discussion

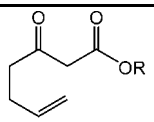
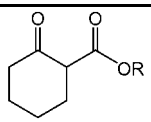
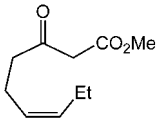
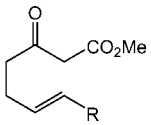
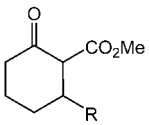
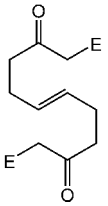
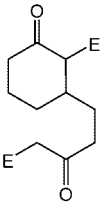
Hydroalkylation of alkenyl β-keto esters: Silyl enol ethers add to unactivated olefins in the presence of a catalytic[11] or stoichiometric amount of $Pd(OAc)_2$[12] and to alkynes in the presence of a catalytic amount of $[W(CO)_5(thf)]$[13] or a stoichiometric amount of $SnCl_4$[14] or $EtAlCl_2$.[15] On the basis of these examples, it appeared likely that the trimethylsilyl enol ether of **4** (**4**-TMS) would be more reactive toward palladium-mediated cyclization than was **4** [Eq. (3)]. However, because **4**-TMS does not possess an acidic hydrogen atom, cyclization of **4**-TMS would not generate the HCl required for protonolysis of palladium–enolate complex **III** (Scheme 1), and therefore, catalytic hydroalkylation would not be realized.[16] Conversely, we reasoned that in situ generation of **4**-TMS from reaction of **4** and Me_3SiCl in the presence of **2** would also generate the HCl required for protonolysis [Eq. (3)].



4 (E = CO_2Me) **4**-TMS (3)

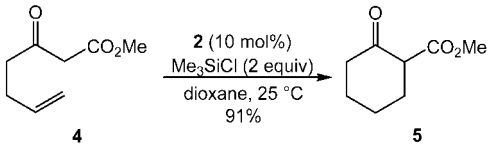
In apparent support of this hypothesis, treatment of **4** with a catalytic amount of **2** (10 mol%) and a stoichiometric amount of Me_3SiCl (2 equiv) in dioxane at room temperature for 8 h led to complete consumption of **4** and isolation of **5** in 91% yield as a single regioisomer [Eq. (4), Table 2, entry 1].[17] However, subsequent studies revealed that Me_3SiCl was not directly involved in hydroalkylation, but

Table 2. Cyclization of 3-butenyl β-keto esters catalyzed by **2** (10 mol%) in the presence of Me_3SiCl (2 equiv) at 25°C in dioxane.

Entry	Substrate[a]	t [h]	Carbocycle	Yield [%]
				
1	R = Me(**4**)	8	**5**	91
2	R = Et	20		82
3	R = Bn	18		83
4	R = *i*Bu	20		82
5		120	**7**	83
				
6	R = Ph	40		93
7	R = Me	14[b]	**17a**	87
				
8		36[b]		83

[a] E = CO_2Me, $[substrate]_0$ = 33 mM. [b] Reaction mixture contained $CuCl_2$ (1 equiv) at 55°C.

rather served as a source of HCl, which was the actual species responsible for facilitating palladium-catalyzed hydroalkylation (see below).



(4)

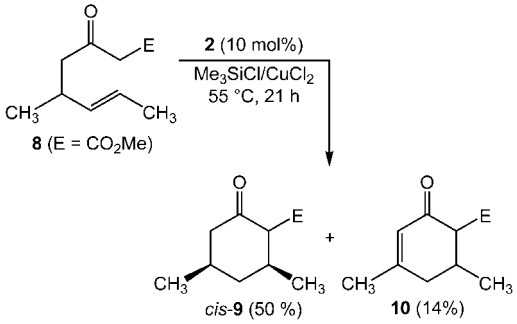
In addition to **4**, ethyl, benzyl, and isobutyl 3-oxo-6-heptenoates underwent intramolecular hydroalkylation in the presence of **2** (10 mol%) and Me_3SiCl (2 equiv) at room temperature to form the corresponding 2-carboalkoxycyclohexanones in >80% yield as single regioisomers (Table 2, entries 2–4). Likewise, (*E*)-methyl 3-oxo-6-nonenoate ((*E*)-**6**), which possesses a terminal olefinic ethyl group, reacted with **2** (10 mol%) and Me_3SiCl (2 equiv) in dioxane at room temperature for two days to form 2-carbomethoxy-3-ethylcyclohexanone (**7**) in 79% isolated yield (Table 3). Attempts

Table 3. Conversion of (*E*)-**6** to **7**.

T [°C]	Oxidant	*t* [h]	Conversion [%]	Yield [%]
25	–	48	100	79
55	–	12	70	–
55	$CuCl_2$	12	100	82

to increase the rate of the conversion of (*E*)-**6** to **7** by raising the reaction temperature to 55°C led to concomitant catalyst decomposition and incomplete conversion (Table 3). We reasoned that catalyst decomposition might be initiated by reduction of Pd^{II} to Pd^0 and if this were the case, an oxidant might prevent catalyst decomposition. Indeed, palladium-catalyzed cyclization of (*E*)-**6** in the presence of both Me_3SiCl (2 equiv) and $CuCl_2$ (1 equiv) at 55°C for 12 h led to complete consumption of (*E*)-**6** to form **7** in 82% yield (Table 3).[17]

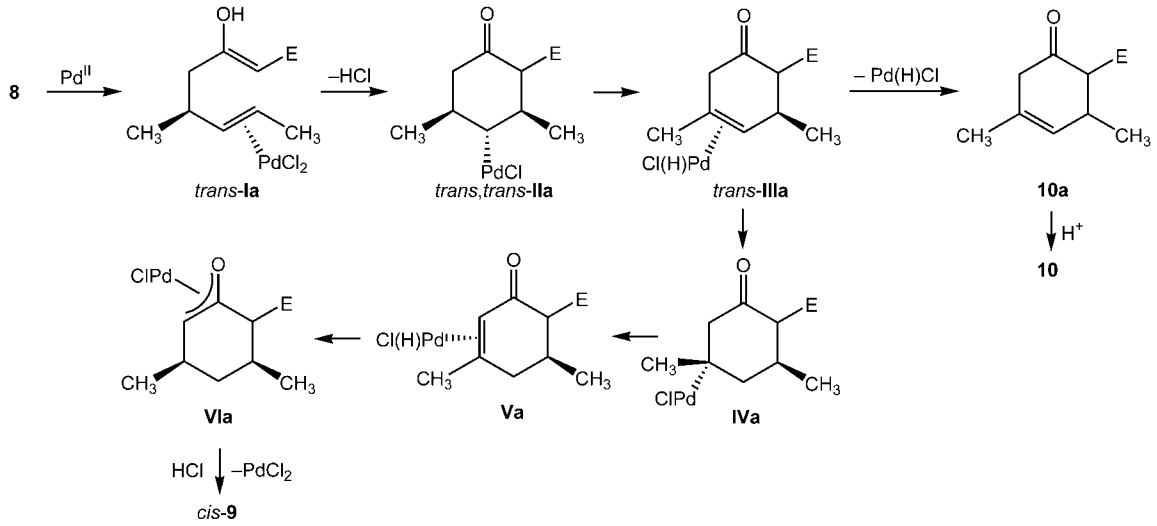
In addition to (*E*)-**6**, a number of 3-butenyl β-keto esters that possessed *cis* or *trans* terminal olefinic substitution underwent palladium-catalyzed cyclization in the presence of Me_3SiCl or $Me_3SiCl/CuCl_2$ to form the corresponding 2,3-disubstituted cyclohexanones in >80% yield with excellent regioselectivity (Table 2, entries 5–8). Palladium-catalyzed conversion of (*Z*)-**6** to **7** was considerably slower than was conversion of (*E*)-**6** to **7**, which is somewhat surprising as *cis*-1,2-disubstituted olefins tend to bind more tightly to transition metals than do *trans*-1,2-disubstituted olefins.[18] Furthermore, this large discrepancy between the reactivity of *cis* and *trans* olefins was not observed in the hydroalkylation of alkenyl α-aryl ketones (see below). Palladium-catalyzed hydroalkylation of 3-butenyl β-keto esters was sensitive to allylic substitution and treatment of (*E*)-**8**, which possessed both an allylic and *trans*-terminal olefinic methyl substituent, with a catalytic amount of **2** in the presence of $Me_3SiCl/CuCl_2$ led to the isolation of cyclohexanone *cis*-**9** in 50% yield as a single diastereomer and cyclohexenone **10** in 14% yield (Scheme 2).[19]



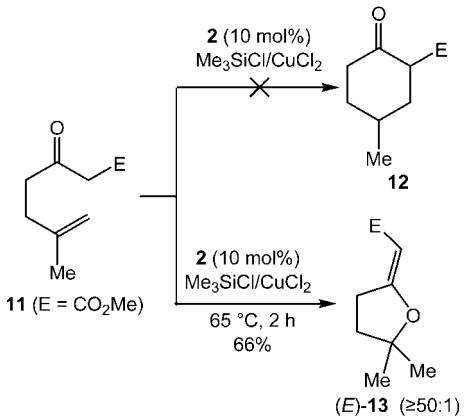
Scheme 2.

Exclusive formation of *cis*-**9** in the palladium-catalyzed cyclization of **8** is in accord with our mechanism for the palladium-catalyzed hydroalkylation of 7-octene-2,4-dione.[2,5] Coordination of palladium to the olefin of **8** should occur preferentially to the face opposite the proximal allylic methyl group to form *trans*-**Ia** (Scheme 3). Given the *anti* stereochemistry of C–C bond formation, cyclization of *trans*-**Ia** would form exclusively *trans,trans*-**IIa** (Scheme 3).[2,5] Because the palladium atom of *trans,trans*-**IIa** is *syn* to the C5 hydrogen atom, palladium can migrate from the C4 carbon atom to the C6 carbon atom of the cyclohexanone by means of iterative β-hydride elimination/addition to form the requisite palladium enolate complex **VIa**, which undergoes protonolysis to form *cis*-**9**. Cyclohexenone **10** could be formed either by displacement from **Va** or by displacement of cyclohexenone **10a** from *trans*-**IIIa** followed by secondary isomerization to **10** (Scheme 3).

Treatment of methyl 6-methyl-3-oxo-6-heptenoate (**11**) with a catalytic amount of **2** in the presence of $Me_3SiCl/CuCl_2$ at 65°C for 2 h formed none of the expected 6-*endo* hydroalkylation product **12**, but instead formed the 5-*exo* hydroalkoxylation product (*E*)-**13** in 66% isolated yield (87% by GC) as a single isomer (Scheme 4).[20] The expected 6-*endo-trig* cyclization of **11** is likely disfavored due to the unfavorable steric interactions associated with formation of a palladium–tertiary-alkyl complex.[21] Attack of the enolic oxygen atom at the internal olefinic carbon atom of **11**, as opposed to attack of the enolic carbon atom, is probably due to the superior overlap of the olefinic π* orbital with the filled oxygen sp^2 orbital, which lies in the C2-C3-C4 plane, as opposed to the enolic π system, which is oriented perpendicular to the C2-C3-C4 plane.[22] Palladium-catalyzed 5-*exo* addition of an enolic oxygen atom to a pendant olefin has been observed previously in the palladium-catalyzed cyclization of cyclopentenol **14** to form bicycle **15** [Eq. (5)].[23] Likewise, we have exploited the 5-*exo* addition of an enolic oxygen atom to a pendant olefin in the pal-

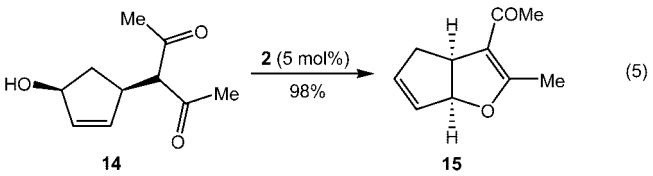


Scheme 3.

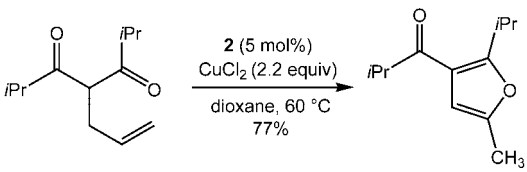


Scheme 4.

ladium-catalyzed conversion of α-allyl β-diketones to form 2,3,5-trisubstituted furans [Eq. (6)].[24]

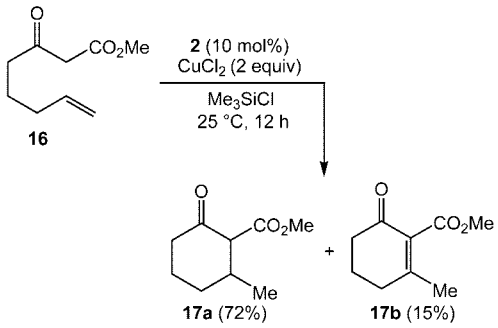


(5)



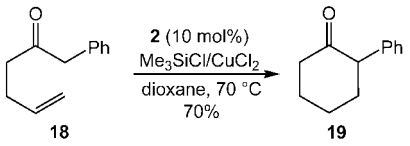
(6)

In contrast to 3-butenyl β-keto esters, which reacted poorly with **2** in the absence of Me_3SiCl,[2] 4-pentenyl β-keto esters were moderately reactive toward **2** in the absence of Me_3SiCl. For example, reaction of methyl 3-oxo-7-octenoate (**16**) with a catalytic amount of **2** (10 mol%) and a stoichiometric amount of $CuCl_2$ (2.5 equiv) in dichloroethane at 70°C for 30 min led to the isolation of 2-carbomethoxy-3-methylcyclohexanone (**17a**) in 47% yield and 2-carbomethoxy-3-methyl-2-cyclohexenone (**17b**) in 27% yield.[4] However, both the reactivity of **16** and the selectivity for the hydroalkylation product **17a** increased upon addition of Me_3SiCl to the reaction mixture. For example, reaction of **16** with a catalytic amount of **2** (10 mol%) in the presence of Me_3SiCl and $CuCl_2$ at room temperature for 12 h led to the isolation of cyclohexanone **17a** in 72% yield and cyclohexenone **17b** in 15% yield [Eq. (7)].



(7)

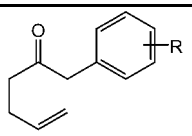
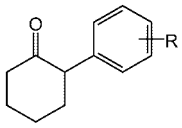
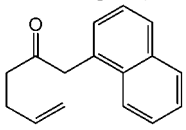
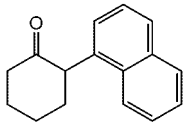
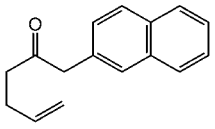
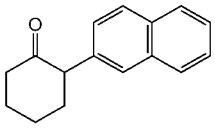
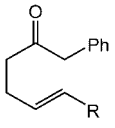
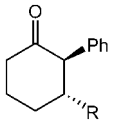
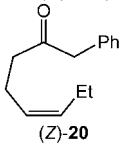
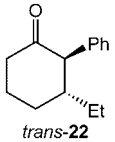
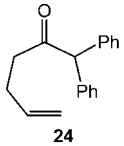
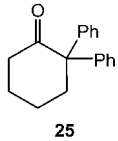
Hydroalkylation of alkenyl α-aryl ketones: The K_a and $K_{enol/ketone}$ of an α-aryl ketone are significantly lower than are the corresponding values for a β-keto ester (Table 1).[6–9] For this reason, it was somewhat surprising that α-aryl 3-butenyl ketones underwent efficient intramolecular hydroalkylation under conditions similar to those employed for the cyclization of β-keto ester (*E*)-**6**, albeit at higher temperatures. For example, treatment of benzyl 3-butenyl ketone (**18**) with a catalytic amount of **2** (10 mol%) and a stoichiometric mixture of Me_3SiCl and $CuCl_2$ at 70°C for 8 h gave 2-phenylcyclohexanone (**19**) in 70% isolated yield as a single regioisomer [Eq. (8)].



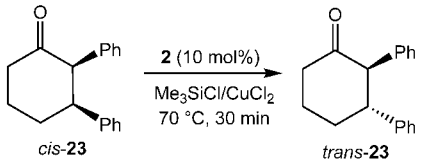
18 19 (8)

Attempted hydroalkylation of **18** in the absence of $CuCl_2$ led to catalyst decomposition and incomplete conversion, as was also observed for (*E*)-**6**. In addition to **18**, α-aryl 3-butenyl ketones that possessed *p*-methyl, *p*-phenyl, *p*-fluoro, *p*-chloro, *p*-bromo, and *p*-iodophenyl groups, *o*-, *m*-, and *p*-trifluoromethylphenyl groups, and 1- and 2-naphthyl groups underwent palladium-catalyzed intramolecular hydroalkylation to form the corresponding 2-arylcyclohexanones in good yield with high regioselectivity (Table 4, entries 1–11). It is worth noting that reactive aryl halides including bromophenyl and iodophenyl were tolerated by the hydroalkylation procedure (Table 4, entries 5 and 6).

Table 4. Cyclization of α-aryl 3-butenyl ketones catalyzed by **2** (10 mol%) in the presence of Me_3SiCl and $CuCl_2$ at 70°C in dioxane.

Entry	Alkenyl ketone	*t* [h]	Cyclohexanone	Yield [%]
				
1	R = *p*-Me	17		62
2	R = *p*-Ph	16		56
3	R = *p*-F	10		81
4	R = *p*-Cl	7		73
5	R = *p*-Br	12		80
6	R = *p*-I	12		65
7	R = *o*-CF_3	12		66
8	R = *m*-CF_3	5		76
9	R = *p*-CF_3	12		76
10		10		74
11		12		71
				
12	(*E*)-**20** (R = Et)	18	*trans*-**22**	77
13	(*E*)-**21** (R = Ph)	36	*trans*-**23**	73
14	 (*Z*)-**20**	12	 *trans*-**22**	83
15	 **24**	12	 **25**	69

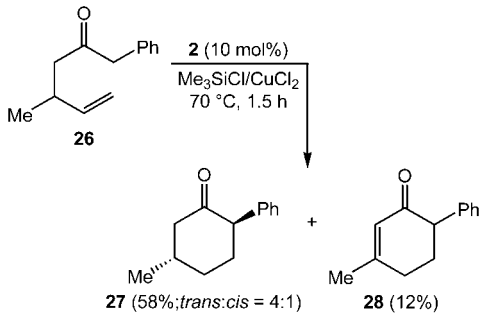
The palladium-catalyzed, Me_3SiCl-mediated hydroalkylation of α-aryl 3-butenyl ketones tolerated terminal olefinic substitution. Treatment of (*E*)-**20**, which possesses a terminal olefinic ethyl group, or (*E*)-**21**, which possesses a terminal olefinic phenyl group, with a catalytic amount of **2** in the presence of $Me_3SiCl/CuCl_2$ led to the formation of cyclohexanones *trans*-**22** or *trans*-**23**, respectively, in >70% yield as single isomers (Table 4, entries 12 and 13). The stereochemistry of *trans*-**22** and *trans*-**23** was established by large (11.6 Hz) splitting of the C2 proton by the *anti* C3 proton in the ^1H NMR spectrum and by single crystal X-ray analysis in the case of *trans*-**23**. Palladium-catalyzed hydroalkylation of **20** was not stereospecific and cyclization of (*Z*)-**20** also formed *trans*-**22** as a single diastereomer in 83% yield (Table 4, entry 14). Although **2** catalyzes the *cis* to *trans* isomerization of olefins that bear an aryl or *tert*-alkyl group,[25] no isomerization of (*Z*)-**20** to (*E*)-**20** was observed throughout complete conversion of (*Z*)-**20** to *trans*-**22**. Rather, the lack of stereospecificity in the palladium-catalyzed hydroalkylation of **20** and **21** can be traced to rapid *cis*–*trans* isomerization of *cis*-**22** and *cis*-**23** under the reaction conditions. For example, treatment of *cis*-**23** with a catalytic amount of **2** (10 mol%) and a stoichiometric mixture of Me_3SiCl and $CuCl_2$ led to quantitative conversion to *trans*-**23** within 30 min at 70°C as determined by GC and ^1H NMR analysis [Eq. (9)].



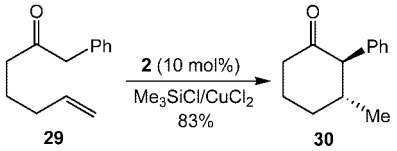
cis-**23** *trans*-**23** (9)

Palladium-catalyzed hydroalkylation of α-aryl 3-butenyl ketones tolerated substitution at the enolic position, and treatment of 1,1-diphenyl-5-hexen-2-one (**24**) with a catalytic amount of **2** in the presence of Me_3SiCl and $CuCl_2$ formed 2,2-diphenylcyclohexanone (**25**) in 69% yield (Table 4, entry 15). Palladium-catalyzed hydroalkylation of α-aryl 3-butenyl ketones was sensitive to allylic substitution, as was the case with alkenyl β-keto esters. For example, reaction of 4-methyl-1-phenyl-5-hexen-2-one (**26**) with a catalytic amount of **2** in the presence of Me_3SiCl and $CuCl_2$ led to the isolation of cyclohexanone **27** in 58% yield as a thermodynamic 4:1 mixture of *trans*:*cis* isomers and cyclohexenone **28** in 12% yield (Scheme 5).

α-Aryl 4-pentenyl ketones also underwent palladium-catalyzed hydroalkylation to form cyclohexanones in good yield with high selectivity. For example, reaction of 1-phenyl-6-hepten-2-one (**29**) with a catalytic amount of **2** and a stoichiometric mixture of $SiMe_3Cl$ and $CuCl_2$ formed *trans*-3-methyl-2-phenylcyclohexanone (**30**) in 83% isolated yield without formation of significant amounts (<5%) of the corresponding cyclohexenone [Eq. (10)].



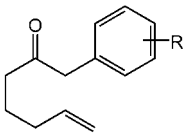
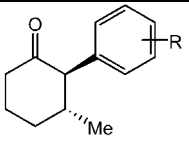
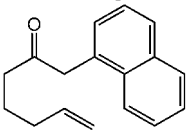
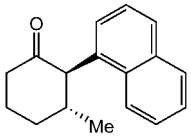
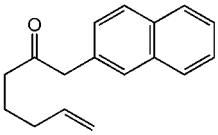
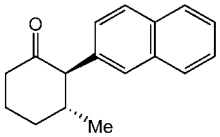
Scheme 5.



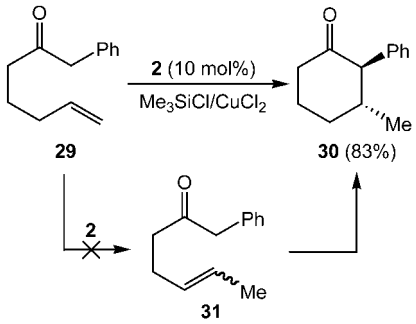
(10)

In addition to **29**, α-aryl 4-pentenyl ketones that possessed *p*-methyl, *p*-fluoro, *p*-chloro, *p*-bromo, *p*-iodo, *m*-trifluoromethyl, and *p*-trifluoromethylphenyl groups, and 1- and 2-naphthyl groups underwent intramolecular hydroalkylation to form the corresponding 2-aryl cyclohexanones in good yield with high regioselectivity (Table 5).

Table 5. Cyclization of α-aryl 4-pentenyl ketones catalyzed by **2** (10 mol%) in the presence of Me_3SiCl and $CuCl_2$ at 70°C in dioxane.

Entry	Alkenyl ketone	*t* [h]	Cyclohexanone	Yield [%]
				
1	R = *p*-Me	12		75
2	R = *m*-CF_3	5		58
3	R = *p*-CF_3	12		68
4	R = *p*-F	6		78
5	R = *p*-Cl	10		71
6	R = *p*-Br	10		67
7	R = *p*-I	20		63
8		34		53
9		24		75

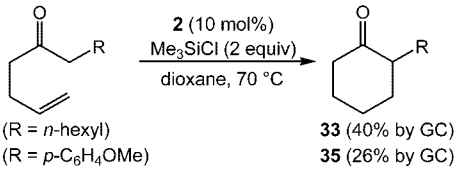
α-Aryl 4-pentenyl ketone **29** and α-aryl 3-butenyl ketones **20** underwent palladium-catalyzed hydroalkylation under comparable conditions at comparable rates. For this reason, and because palladium dichloride complexes catalyze the isomerization of terminal olefins to form internal olefins,[26] we considered that hydroalkylation of **29** might occur by means of initial isomerization to 1-phenyl-5-hepten-2-one (**31**) followed by cyclization to form **30** (Scheme 6). If the



Scheme 6.

conversion of **29** to **30** proceeded through initial isomerization to **31**, compound **31** would probably accumulate during the conversion of **29** to **30**. However, neither **31** nor any other acyclic isomer of **29** was detected by GC/MS analysis throughout complete conversion of **29** to **30**, and for this reason, we conclude that conversion of **29** to **30** occurs by direct hydroalkylation of **29** and not thorugh initial isomerization to **31** (Scheme 6).

Limitations of the silane-mediated protocol: The K_a and $K_{enol/ketone}$ of a dialkyl ketone are $>10^4$ times less favorable than are the corresponding values for an α-aryl ketone (Table 1).[6–9] It is likely for this reason that the palladium-catalyzed, Me_3SiCl-mediated protocol that was applied effectively to the hydroalkylation of alkenyl β-keto esters and α-aryl ketones proved only moderately effective for the hydroalkylation of alkenyl alkyl ketones. For example, treatment of 3-butenyl heptyl ketone (**32**) with a catalytic amount of **2** in the presence of Me_3SiCl and $CuCl_2$ formed 2-hexylcyclohexanone (**33**) in only 40% GC yield [Eq. (11)]. Alkenyl α-aryl ketones that possessed an electron-rich aryl group such as 1-(4-methoxyphenyl)-5-hexene-2-one (**34**) also failed to undergo efficient palladium-catalyzed, silane-mediated hydroalkylation [Eq. (11)].

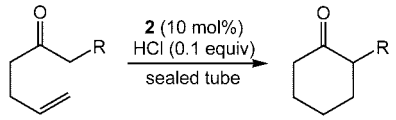


(11)

Behavior of Me_3SiCl under reaction conditions: We had initially hypothesized that Me_3SiCl facilitated the hydroalkylation of alkenyl β-keto ester **4** through the *in situ* formation of the reactive alkenyl trimethylsilyl enol ether **4**-TMS [Eq. (3)]. The failure of alkenyl ketones **32** and **34** to undergo efficient palladium-catalyzed hydroalkylation in the pres-

ence of Me_3SiCl prompted us to probe the validity of this assumption. To this end, a solution of **4** and Me_3SiCl (1:1) in [D_8]dioxane was monitored periodically by ^1H NMR spectroscopy at room temperature. After 30 min, no resonances that could be attributed to **4**-TMS or any other reaction product were detected. Addition of a catalytic amount of **2** (~10 mol%) to the solution of **4** and Me_3SiCl led not to formation of **4**-TMS, but instead to rapid hydrolysis of Me_3SiCl to form a mixture of Me_3SiCl, hexamethyldisiloxane, and HCl.[27] In hindsight, the palladium-catalyzed hydrolysis of Me_3SiCl was not surprising, as **2** also catalyzes the hydrolysis of *tert*-butyldimethyl silyl ethers.[28] Similar results were obtained from ^1H NMR analysis of the reaction of benzyl 3-butenyl ketone (**18**) with Me_3SiCl and **2**.

Given the rapid hydrolysis of Me_3SiCl in the presence of **2**, we considered that perhaps hexamethyldisiloxane or HCl, rather than Me_3SiCl, might be responsible for facilitating palladium-catalyzed hydroalkylation of alkenyl ketones. While hexamethyldisiloxane had no detectable effect on the rate or yield of the palladium-catalyzed hydroalkylation of **4**, treatment of **4** with a mixture of **2** (10 mol%), HCl (0.1 equiv), and $CuCl_2$ (0.3 equiv) in a sealed tube for 12 h at room temperature formed **5** in 83% isolated yield [Eq. (12)]. Likewise, reaction of **18** with sub-stoichiometric amount of **2** (10 mol%), HCl (0.1 equiv), and $CuCl_2$ (0.3 equiv) at 70°C in a sealed tube for 12 h formed **19** in 79% isolated yield [Eq. (12)].[29] On the basis of these experiments, we conclude that Me_3SiCl is not directly involved in palladium-catalyzed hydroalkylation of alkenyl β-keto esters and α-aryl ketones but instead serves as a source of HCl.

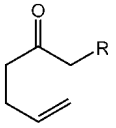
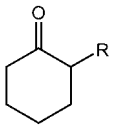
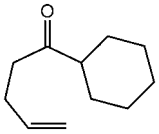
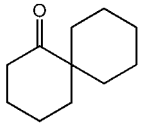
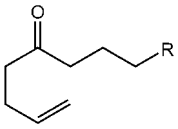
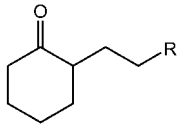
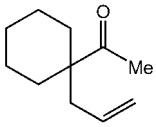
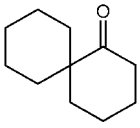
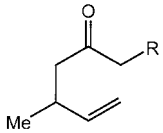
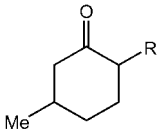


4 (R = CO_2Me)
18 (R = Ph)

5 (83%)
19 (79%)

(12)

Table 6. Cyclization of 3-butenyl ketones catalyzed by **2** (10 mol%) in the presence of $CuCl_2$ (0.3 equiv) and HCl (0.1 equiv) at 70°C in dioxane in a sealed tube from 6–18 h.

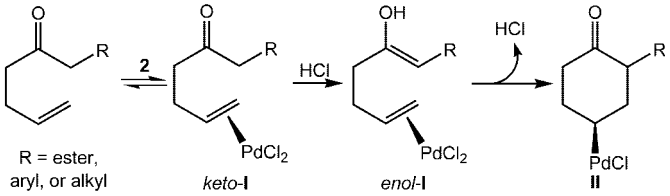
Entry	Alkenyl ketone	Cyclohexanone	Yield(%)
			
1	R = *n*-hexyl (**32**)	**33**	77
2			72[a]
3	*p*-C_6H_4OMe (**34**)	**35**	73
4	R = *n*Bu		65
5	R = Bn		76
6	R = Cy		61
7		 **37**	59
			
8	R = CO_2Me		82
9	R = Cl		55
10	R = OPh		72
11	R = OMe		60
12[b]	 **36**	 **37**	55
13	 **38** (R = *n*hexyl)	 **39**	31 (*trans*) 13 (*cis*)

[a] Me_3SiCl employed in place of HCl. [b] 4.0 equivalents of HCl employed.

Hydroalkylation of alkyl 3-butenyl ketones: Identification of HCl as the active promoter in the palladium-catalyzed, Me_3SiCl-mediated hydroalkylation of alkenyl β-keto esters and α-aryl ketones was significant, because the procedure developed on the basis of this understanding proved effective for the hydroalkylation of alkyl alkenyl ketones and electron-rich alkenyl α-aryl ketones, both of which cyclized inefficiently when we employed our silane-mediated protocol [Eq. (11)]. For example, treatment of **32** with sub-stoichiometric amounts of **2**, HCl, and $CuCl_2$ in a sealed tube for 12 h formed cyclohexanone **33** in 77% isolated yield (86% by GC) (Table 6, entry 1). Likewise, subjection of **34** to these sealed-tube conditions led to the isolation of **35** in 73% yield (Table 6, entry 3). Chlorotrimethylsilane also served effectively as a source of HCl for the conversion of **32** to **33**, provided the reaction was performed in a sealed vessel (Table 6, entry 2).

In addition to **32** and **34**, 3-butenyl pentyl, 3-butenyl phenylethyl, 3-butenyl cyclohexylmethyl, and 3-butenyl cyclohexyl ketone, and alkyl 3-butenyl ketones that possessed a pendant carbomethoxy, chloro, phenoxy, or methoxy group underwent palladium-catalyzed hydroalkylation in the presence of HCl and $CuCl_2$ in a sealed tube to form the corresponding 2-alkylcyclohexanones in 59–76% yield (Table 6, entries 4–11). Reaction of 1-acetyl-1-allylcyclohexane (**36**) with catalytic amount of **2** in the presence of HCl (4 equiv) and $CuCl_2$ (0.6 equiv) at 70°C for 12 h formed a 71:20 mixture of spirocycle **37** and the uncyclized isomerization product (*E*)-1-acetyl-1-(1-propenyl)cyclohexane, from which **37** was isolated in 55% yield (Table 6, entry 12). Reaction of 3-methyl-1-dodecen-5-one (**38**) with sub-stoichiometric amounts of **2**, HCl, and $CuCl_2$ formed a thermodynamic 2.6:1 mixture of *trans*-**39** and *cis*-**39**, from which *trans*-**39** was isolated in 31% yield and *cis*-**39** was isolated in 13% yield (Table 6, entry 13). Neither alkyl 3-butenyl ketones that possessed olefinic substitution, nor alkyl 4-pentenyl ketones underwent efficient palladium-catalyzed hydroalkylation.

Role of HCl in palladium-catalyzed hydroalkylation: The rate of the palladium-catalyzed hydroalkylation of **1** to form **3** was independent of HCl concentration, which rules out turnover-limiting protonolysis of palladium–enolate intermediate **III** (Scheme 1).[2] This result, in conjunction with the results of related kinetic and low-temperature NMR experiments, points to C–C bond formation (**I**→**II**, Scheme 1) as the turnover-limiting step in the conversion of **1** to **3** catalyzed by **2**.[2] Cyclization of **I** to form palladium cyclohexyl intermediate **II** presumably occurs via the enol tautomer (*enol*-**I**) as opposed to the ketone tautomer (*keto*-**I**) (Scheme 7). For this reason, and because enolization of a β-keto ester, α-aryl ketone, or especially dialkyl ketone is slow in the absence of an acid catalyst,[30] we propose that HCl facilitates the palladium-catalyzed hydroalkylation of alkenyl-β-keto esters, α-aryl ketones, and alkyl ketones by catalyzing enolization of the palladium olefin intermediate *keto*-**I** to generate the reactive tautomer *enol*-**I** (Scheme 7).[31]



Scheme 7.

Conclusion

3-Butenyl β-keto esters and α-aryl ketones undergo intramolecular hydroalkylation in the presence of a catalytic amount of $[PdCl_2(CH_3CN)_2]$ (**2**) and a stoichiometric amount of Me_3SiCl or $Me_3SiCl/CuCl_2$ to form cyclohexanones in good yield with high regioselectivity. 4-Pentenyl β-keto esters and α-aryl ketones also cyclize under these conditions to form 2,3-disubstituted cyclohexanones in good yield with high regioselectivity. In contrast to our initial expectations, Me_3SiCl is not directly involved in hydroalkylation, but instead serves as a source of HCl, which we believe facilitates hydroalkylation by catalyzing the enolization of the key palladium olefin complex **I**, thereby increasing the rate of C–C bond formation. Identification of HCl as the active promoter of the palladium-catalyzed hydroalkylation of alkenyl β-keto esters and α-aryl ketones led to the development of an effective protocol for the hydroalkylation of alkyl 3-butenyl ketones that employed sub-stoichiometric amounts of **2**, HCl, and $CuCl_2$ in a sealed tube.

Experimental Section

General methods: Catalytic reactions were performed under an atmosphere of dry nitrogen. NMR spectra were obtained at 400 MHz for ^{1}H NMR spectra and 100 MHz for ^{13}C NMR spectra in $CDCl_3$ at 25 °C unless noted otherwise. IR spectra were obtained on a Bomen MB-100 FT IR spectrometer. 2-Carboalkoxycyclohexanones existed as mixtures of enol and keto tautomers in $CDCl_3$. The predominant tautomer for each carbocycle is noted and NMR data correspond to this predominant tautomer. Gas chromatography was performed on a Hewlett–Parkard 5890 gas chromatograph equipped with a 25 m polydimethylsiloxane capillary column. Flash column chromatography was performed employing 200–400 mesh silica gel (EM). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} eluting with a 5:1 mixture of hexanes and ethyl acetate unless otherwise noted. Elemental analyses were performed by Complete Analysis Laboratories (Parsippany, NJ). 1,4-Dioxane (Aldrich, anhydrous) was used as received. $[PdCl_2(CH_3CN)_2]$ (**2**) was purchased (Aldrich) or was prepared from $PdCl_2$ (Strem) employing a literature procedure.[32] An authentic sample of 2-carbomethoxycyclohexanone (**5**) was purchased from Fluka.

2-Carbomethoxycyclohexanone (5): A solution of **4** (78 mg, 0.50 mmol), Me_3SiCl (0.13 mL, 1.0 mmol), and **2** (13 mg, 0.05 mmol) in dioxane (15 mL) was stirred at room temperature for 8 h. The resulting solution was concentrated under vacuum, treated with aqueous HCl (1 N, 20 mL), and extracted with diethyl ether (3×60 mL). The combined diethyl ether extracts were washed with brine, dried ($MgSO_4$), concentrated, and subjected to chromatography (hexanes/diethyl ether = 75:1) to give **5** (71 mg, 91 %) as a pale yellow oil. Spectral data were identical to an authentic sample (Fluka).

2-Carbomethoxy-3-ethylcyclohexanone (7): A suspension of **2** (15 mg, 0.06 mmol), $CuCl_2{\cdot}2H_2O$ (94 mg, 0.53 mmol), (*E*)-**6** (100 mg, 0.55 mmol), and Me_3SiCl (0.14 mL, 1.1 mmol) in dioxane (15 mL) was stirred at 55 °C for 12 h. The resulting suspension was concentrated under vacuum, treated with aqueous HCl (1 N, 20 mL), and extracted with diethyl ether (3× 60 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), concentrated, and subjected to chromatography (hexanes/diethyl ether = 20:1→5:1) to give **7** (82 mg, 82 %) as a pale yellow oil. TLC: R_f = 0.32; ^{1}H NMR (keto tautomer): δ = 3.75 (s, 3H), 3.14 (d, ^3J(H,H) = 11.2 Hz, 1H), 2.51–2.45 (m, 1H), 2.30–2.23 (m, 1H), 2.07–1.99 (m, 2H), 1.75–1.64 (m, 2H), 1.48–1.36 (m, 2H), 1.31–1.21 (m, 1H), 0.92 ppm (t, ^3J(H,H) = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (keto tautomer): δ = 206.6, 170.7, 63.7, 52.3, 42.8, 41.4, 28.7, 27.9, 25.0, 11.1 ppm; IR (neat): $\tilde{\nu}$ = 1745, 1712, 1649, 1613 cm^{-1} (C=O); elemental analysis calcd (%) for $C_{10}H_{16}O_3$: C 65.19, H 8.75; found: C 65.03, H 8.69.

The remaining cyclohexanones in Table 2 were synthesized employing a procedure analogous to that used to synthesize either **5** or **7**.

Cyclization of methyl 5-methyl-3-oxo-6-octenoate (8): A suspension of **8** (180 mg, 1.0 mmol), Me_3SiCl (220 mg, 2.0 mmol), **2** (26 mg, 0.10 mmol), and $CuCl_2$ (130 mg, 1.0 mmol) in dioxane (10 mL) was stirred at 55 °C for 12 h, quenched with aqueous HCl (1 N, 20 mL), and extracted with diethyl ether (3×60 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and subjected to chromatography (hexanes/diethyl ether = 20:1→2:1) to give *cis*-2-carbomethoxy-3,5-dimethylcyclohexanone (*cis*-**9**; 92 mg, 50 %) as a colorless oil and 6-carbomethoxy-3,5-dimethyl-2-cyclohexenone (**10**; 25 mg, 14 %) as white crystals. The stereochemistry and stereochemical purity of *cis*-**9** was determined by ^{1}H and ^{13}C NMR analysis, respectively, of *cis*-3,5-dimethylcyclohexanone generated by decarboalkoxylation of *cis*-**9** employing a method similar to that reported by Johnson.[19,33] To this end, a mixture of *cis*-**9** (92 mg, 0.5 mmol), NaCl (60 mg, 1.0 mmol), and H_2O (0.5 mL, 28 mmol) in DMSO (2 mL) was stirred at 170 °C for 2 h, diluted with water (20 mL), and extracted with pentane (2×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under vacuum. The resulting oily residue was filtered through a plug of silica and eluted with pentane/diethyl ether (1:1 mixture, 20 mL), to give *cis*-3,5-dimethylcyclohexanone (50 mg, 79 %) as a colorless oil, which was identified on the basis of ^{1}H and ^{13}C NMR spectroscopy.[19] The ^{13}C NMR spectrum of *cis*-3,5-dimethylcyclohexanone indicated >95 % isomeric purity.[19]

Data for *cis*-9: TLC: R_f = 0.42; ^{1}H NMR (keto tautomer): δ = 3.75 (s, 3H), 2.98 (d, ^3J(H,H) = 12.0 Hz, 1H), 2.44–2.40 (m, 1H), 2.30–2.20 (m, 1H), 1.83 (m, 3H), 1.19–1.10 (m, 1H), 1.02 (d, ^3J(H,H) = 6.0 Hz, 3H), 1.01 ppm (d, ^3J(H,H) = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (keto tautomer): δ = 206.6, 170.7, 64.7, 52.2, 49.4, 41.9, 35.9, 33.1, 22.5, 21.3 ppm; IR (neat): $\tilde{\nu}$ = 1745, 1711, 1609 cm^{-1} (C=O); elemental analysis calcd (%) for $C_{10}H_{16}O_3$: C 65.19, H 8.75; found: C 65.37, H 8.82.

Data for 10: M.p. 40–42 °C; TLC: $R_f = 0.08$; ^{1}H NMR: $\delta = 5.91$ (br s, 1H), 3.77 (s, 3H), 3.03 (d, ^3J(H,H) = 12.0 Hz, 1H), 2.49–2.61 (m, 1H), 2.38 (dd, ^3J(H,H) = 4.8, ^2J(H,H) = 18.8 Hz, 1H), 2.09 (qdd, ^4J(H,H) = 1.2, ^3J(H,H) = 10.4, ^2J(H,H) = 18.4 Hz, 1H), 1.96 (s, 3H), 1.05 ppm (d, ^3J(H,H) = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR: $\delta = 194.4$, 170.9, 162.3, 125.6, 60.9, 52.3, 38.6, 32.8, 24.5, 20.0 ppm; IR (neat): $\tilde{\nu} = 1742$, 1667 cm^{-1} (C=O); HRMS: m/z calcd for $C_{10}H_{14}O_3$: 182.0943 (found: 182.0954).

(*E*)-Methyl (5,5-dimethyldihydrofuran-2-ylidene)acetate ((*E*)-13):[34] A suspension of **11** (100 mg, 0.60 mmol), **2** (16 mg, 0.06 mmol), $CuCl_2$ (40 mg, 0.30 mmol), and Me_3SiCl (0.15 mL, 1.20 mmol) in dioxane (10 mL) was stirred at 65 °C for 2 h, cooled to room temperature, and concentrated under vacuum. The resulting oily residue was subjected to chromatography (hexanes/diethyl ether = 25:1→12:1) to give (*E*)-**13** (66 mg, 66 %) as a colorless oil.

2-Phenylcyclohexanone (19): A suspension of **18** (87 mg, 0.50 mmol), Me_3SiCl (0.19 mL, 1.50 mmol), **2** (13 mg, 0.05 mmol), and $CuCl_2$ (67 mg, 0.50 mmol) in dioxane (10 mL) was stirred at 70 °C for 8 h. The reaction mixture was filtered through a plug of silica gel and eluted with diethyl ether. The resulting solution was concentrated under vacuum and subjected to chromatography (hexanes/diethyl ether = 25:1→15:1) to give **19** (61 mg, 70 %) as a pale yellow solid.

The remaining cyclohexanones in Tables 4 and 5 were synthesized employing a procedure analogous to that used to synthesize **19** unless noted otherwise.

***cis*-2,3-Diphenylcyclohexanone (*cis*-23)**: A suspension of phenyl magnesium chloride (2.0 M in THF, 1.5 mL, 3.0 mmol) and CuI (32 mg, 0.17 mmol) in THF (10 mL) was stirred at 0 °C for 30 min and then treated with a solution of 2-phenyl-2-cyclohexenone (0.34 g, 2.0 mmol) in THF (2 mL). The resulting suspension was stirred at room temperature for 12 h, poured into aqueous HCl (1 N), and extracted with diethyl ether. The combined organic extracts were washed with 10 % aqueous $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated under vacuum. The resulting residue was subjected to chromatography (hexanes/diethyl ether = 40:1→15:1) to give *cis*-**23** (70 mg, 14 %) as a white solid. M.p. 85–86 °C; TLC: $R_f = 0.50$; ^{1}H NMR: $\delta = 7.20$–7.12 (m, 6H), 7.03–6.99 (m, 4H), 4.05 (d, ^3J(H,H) = 5.6 Hz, 1H), 3.62 (m, 1H), 2.79–2.72 (m, 1H), 2.64–2.58 (m, 1H), 2.32–2.16 (m, 3H), 1.99–1.90 ppm (m, 1H); ^{13}C{^{1}H} NMR: $\delta =$ 211.0, 141.9, 136.5, 130.0, 128.5, 128.4, 128.3, 127.0, 126.8, 61.8, 48.7, 40.8, 28.6, 24.0 ppm; IR (neat): $\tilde{\nu} = 1708$, 1679 cm^{-1} (C=O); elemental analysis calcd (%) for $C_{18}H_{18}O$: C 86.36, H 7.25; found: C 86.27, H 7.36.

Isomerization of *cis*-23 under reaction conditions: A suspension of *cis*-**23** (58 mg, 0.23 mmol), Me_3SiCl (0.12 mL, 0.94 mmol), **2** (8 mg, 0.03 mmol), and $CuCl_2$ (42 mg, 0.32 mmol) in dioxane (6 mL) was stirred at 70 °C. After 30 min, GC analysis revealed complete (≥ 98 %) conversion to *trans*-**23**. The reaction mixture was cooled to room temperature, filtered through a plug of silica gel, and eluted with diethyl ether. The resulting solution was concentrated to give *trans*-**23** (56 mg, 97 %) as a pale yellow solid that was both chemically and isomerically pure (≥ 95 %) by ^{1}H NMR analysis.

2-Hexylcyclohexanone (33): A suspension of **2** (13 mg, 0.05 mmol), $CuCl_2$ (20 mg, 0.15 mmol), HCl (4 N in dioxane, 13 μL, 0.05 mmol), and **32** (91 mg, 0.50 mmol) in dioxane (6 mL) was stirred at 70 °C in a sealed tube for 12 h. The resulting mixture was filtered through a short plug of silica gel and eluted with hexanes/diethyl ether (1:1, 30 mL). The resulting solution was concentrated under vacuum and the residue was subjected to chromatography (hexanes/diethyl ether = 20:1→10:1) to give **33**[35] (70 mg, 77 %) as a pale yellow oil.

The remaining cyclohexanones in Table 6 were synthesized employing a procedure analogous to that used to synthesize **33**.

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