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OXIDATIVE ADDITION OF CHLORO- AND DICHLOROACETIC ACID TO ALKENES TO GIVE α-CHLORO- AND α,α-DICHLORO-BUTYROLACTONES WITH MANGANESE(III) ACETATE†

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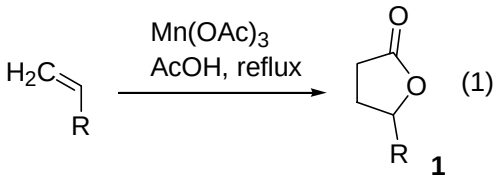
Abstract – Oxidative addition of chloroacetic acid and dichloroacetic acid to alkenes with $Mn(OAc)_3$ to give α-chloro- and α,α-dichlorobutyrolactones proceeds in moderate to good yield in MeCN containing one equivalent of the sodium salt of the carboxylic acid.

INTRODUCTION

The reaction of alkenes with 2 equivalents of $Mn(OAc)_3$ in AcOH at reflux to give lactone (**1**) (see equation 1) first reported by Bush and Finkbeiner, and Heiba and Dessau is a versatile method for the annulation of a γ-lactone to an alkene.[1-3] The rate determining step in the reaction is the loss of a proton from manganese(III) acetate (**2**) to give enolate (**3**) (see equation 2).[4] Rapid loss of Mn(II) gives radical (**4**), which adds to the alkene to give radical (**5**). Oxidation of **5** with loss of Mn(II) gives lactone (**1**).

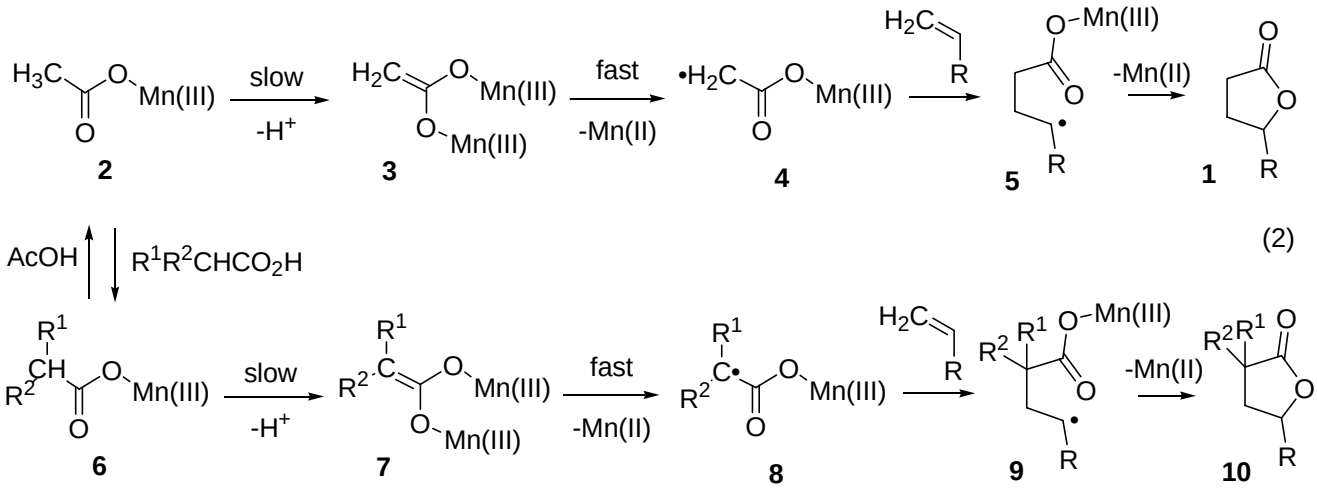


(1)

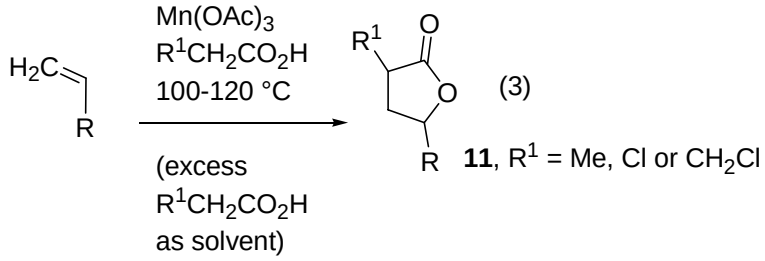
1

Since enolization is the slow step, acids with a more acidic α-proton should be more reactive than acetic acid. Exchange of $R^1R^2CHCO_2H$ with $Mn(OAc)_3$ should give Mn(III) carboxylate (**6**). Loss of a proton from **6** to give enolate (**7**) should be faster than loss of a proton from acetate (**2**) to give enolate (**3**). Enolate (**7**) will rapidly lose Mn(II) to give radical (**8**), which will add to the alkene to give radical (**9**), which will be oxidized with loss of Mn(II) to give α-substituted lactone (**10**). Acids with much more acidic α-protons

† Dedicated to Professor Leo Paquette on the occasion of his 70th birthday



such as cyanoacetic acid and ethyl hydrogen malonate add to alkenes in acetic acid at 23-70 ºC.[5,6] However, acids with only slightly more acidic α-protons such as chloroacetic and 3-chloropropanoic acid do not enolize enough faster to compete with enolization of the solvent, acetic acid. For instance, the alpha proton of chloroacetic acid is 1,000 times more acidic than the alpha proton of acetic acid, but chloroacetic acid reacts with $Mn(OAc)_3$ only 11 times faster than acetic acid.[4a] Lactone (**11**) can be formed by the reaction of other carboxylic acids with alkenes and $Mn(OAc)_3$ in moderate yield if a large excess of the carboxylic acid is used as the solvent (see equation 3).[1,5] The need to use a vast excess of the carboxylic acid as the solvent has limited the utility of this route to α-substituted lactones (**11**).

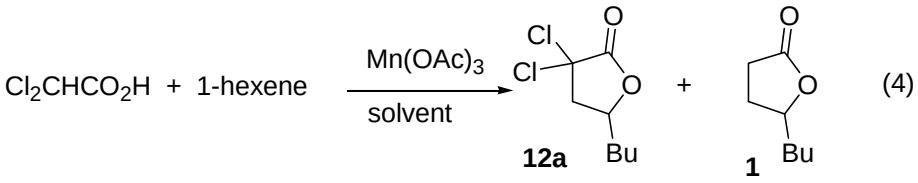


During the course of our study of Mn(III)-based oxidative free-radical cyclizations, we found that many solvents other than acetic acid can be used for these reactions.[7] We decided to explore whether the oxidative addition of dichloroacetic and chloroacetic acid to alkenes with $Mn(OAc)_3$ to give α,α-dichlorolactones (**12**) and α-chlorolactones (**13**) could be carried in an inert solvent without the need to use excess carboxylic acid as solvent. Lactones (**12**) and (**13**) have been previously prepared in moderate yield by radical reactions of trichloroacetic or dichloroacetic acid and esters to alkenes initiated by CuCl, $[CpMo(CO)_3]_2$, or $(Ph_3P)_3RuCl_2$ at high temperatures.[8]

RESULTS AND DISCUSSION

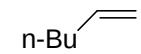
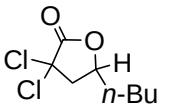
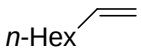
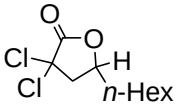
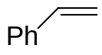
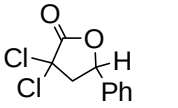
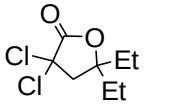
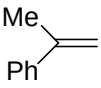
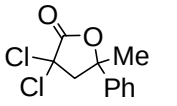
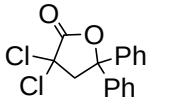
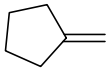
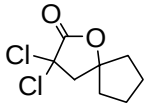
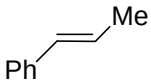
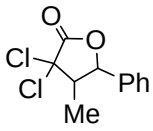
As expected, reaction of 1-hexene, 1 equivalent of dichloroacetic acid and 2 equivalents of $Mn(OAc)_3•2H_2O$ in AcOH at 85 ºC for 2 days afforded 24% of lactone (**1**) and only 6% of the desired lactone (**12a**) (see equation 4). Even though the alpha proton of dichloroacetic acid is more acidic than that

of acetic acid,[9] **1** is still the major product since acetic acid is present in such great excess as solvent. No lactone (**12a**) was formed from 1-hexene, dichloroacetic acid, and anhydrous $Mn(OAc)_3$[10] in EtOH, DMF, trifluoroethanol, benzene, or 9:1 MeCN/TFA at 70-100 ºC.



Finally, we were pleased to find that lactone (**12a**) was formed in 33% yield from 1-hexene, 2 equivalents of dichloroacetic acid and 2 equivalents of anhydrous $Mn(OAc)_3$ in MeCN at 95 ºC in a sealed tube for 3 days. No lactone (**1**) was formed in MeCN. The yield of **12a** decreased from 33% to 28% with $Mn(OAc)_3 \cdot 2H_2O$. Addition of one equivalent of sodium dichloroacetate to the reaction mixture increased the yield of **12a** to 45% and decreased the time required for consumption of Mn(III) to 1.5 days. The yield

Table 1. Preparation of α,α-Dichlorobutyrolactones (**12**)[a]

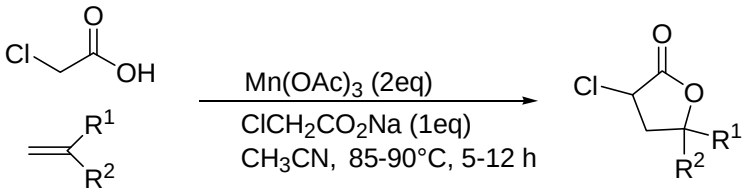
Entry	Alkene	Time	Product		Yield[b]
a		40 h		**12a**	45%
b		43 h		**12b**	48%
c		48 h		**12c**	62% (90%)
d		46 h		**12d**	36%
e		40 h		**12e**	81% (96%)
f		48 h		**12f**	82% (95%)
g		48 h		**12g**	27%
h		30 h		**12h**[c]	30% (73%)

[a] A 0.1 M solution of alkene in MeCN containing 1 equiv. of Cl_2HCCO_2Na, and 2 equiv. of Cl_2CHCO_2H and $Mn(OAc)_3$ was heated in a sealed tube at 95-100 °C for the indicated time. [b] Isolated yield. Yield in parentheses is based on reacted alkene. [c] 26:1 *trans*/*cis* mixture.

of **12a** decreased from 45% to 22% with three equivalents of sodium dichloroacetate. No lactone (**12a**) was formed from two equivalents of sodium dichloroacetate in the absence of dichloroacetic acid. This suggests that the 2:1 mixture of dichloroacetic acid to sodium dichloroacetate provides near optimal pH for lactone formation.

These optimized conditions were then used to survey the scope of the reaction with regard to the alkene as shown in Table 1. α,α-Dichlorolactones (**12**) were obtained in 27-82% yield. As expected for an electrophilic radical, MnO_2CCCl_2•, the reactions proceed in 62-82% yield with nucleophilic alkenes in which one end is unsubstituted and therefore sterically accessible and the other end has a phenyl substituent (Entries c, e, and f). Terminal and 1,1-disubstituted alkyl substituted alkenes afford 27-48% of lactone (**12**) (Entries a, b, d, and g). With the exception of β-methylstyrene (Entry h), internal alkenes give poor yields of lactone (**12**). The structures were assigned by comparison with authentic samples.[8] The stereochemistry of lactone (**12h**) was assigned based on vicinal coupling constants for the *trans* (9.8 Hz) and *cis* (5.5 Hz) isomers.[11]

We also briefly investigated the reactions of alkenes with five equivalents of chloroacetic acid, two equivalents of $Mn(OAc)_3$ and one equivalent of sodium chloroacetate in acetonitrile (see equation 5). Although, consumption of Mn(III) was complete in 5-12 h, the yield of α-chlorobutyrolactones (**13a-c**) was lower than for the analogous α,α-dichlorobutyrolactone (**12**). The structures were assigned by comparison with authentic samples.[6b,8]



(5)

13a, R^1 = H, R^2 = *n*-Bu (22%, 1:1 trans/cis)
13b, R^1 = H, R^2 = Ph (58%, 1:1 trans/cis)
13c, $R^1 = R^2$ = Ph (38%, 84% based on recoved $Ph_2C{=}CH_2$)

In conclusion, we have shown that oxidative addition of chloroacetic acid and dichloroacetic acid to a variety of alkenes to give dichlorolactones (**12**) and chlorolactones (**13**), respectively, can be successfully carried out with $Mn(OAc)_3$ and one equivalent of the sodium salt of the acid in MeCN at 85-100 °C.

EXPERIMENTAL

General. All reactions were performed in oven-dried resealable tubes. NMR spectra were recorded at 400 MHz in $CDCl_3$. Chemical shifts are reported in δ and coupling constants in Hz. IR spectra were reported in cm^{-1}. Anhydrous $Mn(OAc)_3$ was prepared from commercial $Mn(OAc)_3 \cdot 2H_2O$ (Fisher) by drying over P_2O_5 for 1 week under vacuum.[10]

5-Butyl-3,3-dichlorodihydro-2(3*H*)-furanone (12a). NaO_2CCHCl_2 (75.5 mg, 0.5 mmol) and anhydrous $Mn(OAc)_3$ (232 mg, 1 mmol) were added to 5 mL of dry MeCN in a resealable tube at rt. Cl_2CHCO_2H (128 mg, 1 mmol) and 1-hexene (42 mg, 0.5 mmol) were added to the suspension under nitrogen. After sealing, the tube was immersed in an oil bath at 95-100 °C. The reaction was stirred magnetically at this temperature until the brown color of Mn(III) disappeared (40 h). Upon cooling to rt, the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 50:1 hexanes/EtOAc) to give 48 mg (45%) of lactone (**12a**) as a colorless oil: ^{1}H NMR 4.65-4.61 (m, 1H), 3.17 (dd, 1H, J = 14.1, 4.9), 2.61 (dd, 1,H J = 14.1, 9.7), 1.87-1.26 (m, 6H), 0.94 (t, 3H, J = 7.3); ^{13}C NMR 167.7, 78.1, 77.5, 50.2, 33.7, 26.9, 22.2, 13.8; IR (neat) 1795. The ^{1}H NMR spectral data are identical to those reported previously.[8b]

3,3-Dichloro-5-hexyldihydro-2(3*H*)-furanone (12b) was prepared analogously to **12a** from NaO_2CCHCl_2 (76 mg, 0.5 mmol), anhydrous $Mn(OAc)_3$ (232 mg, 1 mmol), Cl_2CHCO_2H (128 mg, 1 mmol) and 1-octene (85 μL, 0.5 mmol) in 5 mL of dry MeCN. Flash chromatography (silica gel, 40:1 hexanes/EtOAc) of the crude product gave 70 mg (48%) of lactone (**12b**) as a colorless oil: ^{1}H NMR 4.62 (ddt, 1H, J = 9.8, 4.9, 6.8), 3.16 (dd, 1H, J = 14.0, 4.9), 2.61 (dd, 1H, J = 14.0, 9.8), 1.87-1.28 (m, 10H), 0.89 (t, 3H, J = 7.3); ^{13}C NMR 167.8, 78.1, 77.5, 50.2, 34.1, 31.5, 28.7, 24.8, 22.4, 14.0; IR (neat) 1795. The ^{1}H NMR spectral data are identical to those reported previously.[8b]

3,3-Dichlorodihydro-5-phenyl-2(3*H*)-furanone (12c) was prepared analogously to **12a** from NaO_2CCHCl_2 (76 mg, 0.5 mmol), anhydrous $Mn(OAc)_3$ (232 mg, 1 mmol), Cl_2CHCO_2H (128 mg, 1 mmol) and styrene (64 μL, 0.5 mmol) in 5 mL of dry acetonitrile. Flash chromatography (silica gel, 100:1~25:1 hexanes/EtOAc) of the crude product gave 16 mg of styrene followed by 72 mg (62%, 90% based on recovered styrene) of lactone (**12c**) as a colorless oil: ^{1}H NMR 7.45-7.34 (m, 5H), 5.62 (dd, 1H, J = 10.3, 4.9), 3.43 (dd, 1H, J = 14.6, 4.9), 2.93 (dd, 1H, J = 14.6, 10.3); ^{13}C NMR 167.4, 135.4, 129.5, 129.0 (2 C), 125.7 (2 C), 78.5, 77.4, 52.2; IR (neat) 1798. The ^{1}H NMR spectral data are identical to those reported previously.[8f]

3,3-Dichloro-5,5-diethyldihydro-2(3*H*)-furanone (12d) was prepared analogously to **12a** from NaO_2CCHCl_2 (76 mg, 0.5 mmol), anhydrous $Mn(OAc)_3$ (232 mg, 1 mmol), Cl_2CHCO_2H (128 mg, 1 mmol) and 2-ethyl-1-butene (61 μL, 0.5 mmol) in 5 mL of dry MeCN. Flash chromatography (silica gel, 25:1 hexanes/EtOAc) of the crude product gave 38 mg (36%) of lactone (**12d**) as a colorless oil: ^{1}H NMR 3.02 (s, 2H), 1.93-1.76 (m, 4H), 0.96 (t, 6H, J = 7.3); ^{13}C NMR 168.3, 88.0, 77.4, 51.7, 30.4 (2 C), 7.6 (2 C); IR (neat) 1791. The ^{1}H NMR spectral data are identical to those reported previously.[8d]

3,3-Dichlorodihydro-5-methyl-5-phenyl-2(3*H*)-furanone (12e) was prepared analogously to **12a** from NaO_2CCHCl_2 (76 mg, 0.5 mmol), anhydrous $Mn(OAc)_3$ (232 mg, 1 mmol), Cl_2CHCO_2H (128 mg, 1 mmol) and α-methylstyrene (65 μL, 0.5 mmol) in 5 mL of dry MeCN. Flash chromatography (silica gel, 100:1 to 20:1 hexanes/EtOAc) of the crude product gave 18 mg of α-methylstyrene followed by 99 mg (81%, 96% based on recovered α-methylstyrene) of lactone **(12e**) as a colorless oil: ^{1}H NMR 7.40-7.29 (m, 5H), 3.49 (d, 1H, J = 15.0), 3.36 (d, 1H, J = 15.0), 1.83 (s, 3H); ^{13}C NMR 167.6, 142.7, 128.7 (2 C), 128.1, 123.6 (2 C), 85.0, 76.7, 56.4, 30.2; IR (neat) 1797. The ^{1}H NMR spectral data are identical to those reported previously.[8f]

3,3-Dichlorodihydro-5,5-diphenyl-2(3*H*)-furanone (12f) was prepared analogously to **12a** from NaO_2CCHCl_2 (76 mg, 0.5 mmol), anhydrous $Mn(OAc)_3$ (232 mg, 1 mmol), Cl_2CHCO_2H (128 mg, 1 mmol) and 1,1-diphenylethylene (88 μL, 0.5 mmol) in 5 mL of dry MeCN. Flash chromatography (silica gel, 100:1 to 20:1 hexanes/EtOAc) of the crude product gave 12 mg of 1,1-diphenylethylene followed by 126 mg (82%, 95% based on recovered 1,1-diphenylethylene) of lactone (**12f**) as a white solid: mp 94-95 °C (lit.,[8a] mp 96-98 °C); ^{1}H NMR 7.40-7.24 (m, 10H), 3.88 (s, 2H); ^{13}C NMR 167.2, 141.5 (2 C), 128.7(2 C), 128.4 (4 C), 124.9 (4 C), 87.4, 76.3, 55.7; IR (neat) 1791.

3,3-Dichloro-1-oxaspiro[4.4]nonan-2-one (12g) was prepared analogously to **12a** from NaO_2CCHCl_2 (76 mg, 0.5 mmol), anhydrous $Mn(OAc)_3$ (232 mg, 1 mmol), Cl_2CHCO_2H (128 mg, 1 mmol) and methylenecyclopentane (52 μL, 0.5 mmol) in 5 mL of dry MeCN. Flash chromatography (silica gel, 50:1 hexanes/EtOAc) of the crude product gave 38 mg (27%) of lactone (**12g**) as a colorless oil: ^{1}H NMR 3.14 (s, 2H), 2.22-2.17 (m, 2H), 1.90-1.74 (m, 6H); ^{13}C NMR 167.7, 92.8, 77.5, 53.3, 39.0 (2 C), 23.6 (2 C); IR (neat) 1790. *Anal.* Calcd for $C_8H_{10}Cl_2O_2$: C, 45.96; H, 4.82; Cl, 33.91. Found: C, 45.64; H, 4.57; Cl, 33.84.

3,3-Dichlorodihydro-4-methyl-5-phenyl-2(3*H*)-furanone (12h) was prepared analogously to **12a** from NaO_2CCHCl_2 (76 mg, 0.5 mmol), anhydrous $Mn(OAc)_3$ (232 mg, 1 mmol), Cl_2CHCO_2H (128 mg, 1 mmol) and *trans*-β-methylstyrene (65 μL, 0.5 mmol) in 5 mL of dry MeCN. Flash chromatography (silica gel, 100:1 to 20:1 hexanes/EtOAc) of the crude product gave 35 mg of *trans*-β-methylstyrene followed by 37 mg (30%, 73% based on recovered *trans*-β-methylstyrene) of lactone (**12h**) as a 26:1 mixture of *trans* and *cis* isomers. *Anal.* Calcd for $C_{11}H_{10}Cl_2O_2$: C, 53.90; H, 4.11; Cl, 28.93. Found: C, 54.03; H, 3.92; Cl, 28.74.

Data for *trans*-**12h**: ^{1}H NMR 7.45-7.33 (m, 5H), 5.04 (d, 1H, J = 9.8), 2.78 (dq, 1H, J = 9.8, 7.0), 1.29 (d, 3H, J = 7.0); ^{13}C NMR 167.7, 134.4, 130.1, 129.3 (2 C), 126.7 (2 C), 84.8, 82.9, 55.8, 9.2; IR (neat) 1803. Partial data for *cis*-**12h**: ^{1}H NMR 7.45-7.33 (m, 5H), 5.93 (d, 1H, J = 5.5), 3.28 (dq, 1H, J = 7.3, 5.5), 0.87 (d, 3H, J = 7.3).

5-Butyl-3-chlorodihydro-2(3*H*)-furanone (13a). $ClCH_2CO_2H$ (235 mg, 2.5 mmol), NaO_2CCH_2Cl (58 mg, 0.5 mmol) and anhydrous $Mn(OAc)_3$ (232 mg, 1 mmol) were added to 5 mL of dry MeCN in a resealable tube at rt. 1-Hexene (42 mg, 0.5 mmol) was added to the suspension *via* syringe under nitrogen. After sealing, the tube was immersed in an oil bath at 85-90 °C. The reaction was stirred at this temperature until the brown color of Mn(III) disappeared (5 h). Upon cooling to rt, the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL), the combined organic extracts were washed with saturated $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 50:1 hexanes/EtOAc) to give 20 mg (22%) of lactone **(13a**) as a 1:1 mixture of *trans* and *cis* isomers.[8d]

Data for *trans*-**13a**: ^{1}H NMR 4.79-4.72 (m, 1H), 4.43 (dd, 1H, J = 6.7, 2.5), 2.52 (ddd, 1H, J = 14.1, 5.6, 2.5), 2.31 (ddd, 1H, J = 14.1, 8.5, 6.7), 1.88-1.25 (m, 6H), 0.93 (t, 3H, J = 7.0); IR (neat) 1791.

Data for *cis*-**13a**: ^{1}H NMR 4.54 (dd, 1H, J = 10.4, 8.5), 4.48-4.40 (m, 1H), 2.92 (ddd, 1H, J = 12.7, 8.5, 6.1), 2.13 (ddd, 1H, J = 12.7, 10.4, 9.8), 1.88-1.25 (m, 6H), 0.93 (t, 3H, J = 7.0); IR (neat) 1791.

3-Chlorodihydro-5-phenyl-2(3*H*)-furanone (13b) was prepared analogously to **13a** from $ClCH_2CO_2H$ (235 mg, 2.5 mmol), NaO_2CCH_2Cl (58 mg, 0.5 mmol), anhydrous $Mn(OAc)_3$ (232 mg, 1 mmol) and styrene (64.3 μL, 0.5 mmol) in 5 mL of dry MeCN for 9 h. Flash chromatography (silica gel, 25:1 hexanes/EtOAc) gave 57 mg (58%) of lactone (**13b**) as a 1:1 mixture of *trans* and *cis* isomers.

Data for *trans*-**13b**: ^{1}H NMR 7.45-7.34 (m, 5H), 5.76 (dd, 1H, J = 8.6, 6.1), 4.50 (dd, 1H, J = 6.7, 2.5), 2.81 (ddd, 1H, J = 14.3, 6.1, 2.5), 2.63 (ddd, 1H, J = 14.3, 8.6, 6.7); IR (neat) 1791. The ^{1}H NMR spectral data are identical to those reported previously.[8e,8f]

Data for *cis*-**13b**: ^{1}H NMR 7.45-7.34 (m, 5H), 5.43 (dd, 1H, J = 9.8, 5.5), 4.71 (dd, 1H, J = 11.0, 8.6), 3.20 (ddd, 1H, J = 13.6, 8.6, 5.5), 2.44 (ddd, 1H, J = 13.6, 11.0, 9.8,); IR (neat) 1791. The ^{1}H NMR spectral data are identical to those reported previously.[8e,8f]

3-Chlorodihydro-5,5-diphenyl-2(3*H*)-furanone (13c) was prepared analogously to **13a** from $ClCH_2CO_2H$ (235 mg, 2.5 mmol), NaO_2CCH_2Cl (58 mg, 0.5 mmol), anhydrous $Mn(OAc)_3$ (232 mg, 1 mmol) and 1,1-diphenylethylene (88 μL, 0.5 mmol) in 5 mL of dry MeCN for 12 h. Flash chromatography (silica gel, 100:1~25:1 hexanes/EtOAc) gave 50 mg of 1,1-diphenylethylene followed by 52 mg (38%, 84% based on recovered 1,1-diphenylethylene) of lactone (**13c**) as a white solid: mp 90-92 °C (lit., [6b] mp 90.0-91.4 °C); ^{1}H NMR 7.43-7.29 (m, 10H), 4.51 (dd, 1H, J = 8.0, 11.0), 3.61 (dd, 1H, J = 8.0, 13.5), 3.03 (dd, 1H, J = 11.0, 13.5); ^{13}C NMR 171.3, 142.3, 141.2, 128.9 (2 C), 128.7 (2 C), 128.4, 128.3, 125.2 (4 C), 87.6, 51.2, 45.5; IR (neat) 1791. The ^{1}H NMR spectral data are identical to those reported previously.[6b]

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