Stereocontrol in Intermolecular Dirhodium(II)-Catalyzed Carbonyl Ylide Formation and Reactions. Dioxolanes and Dihydrofurans

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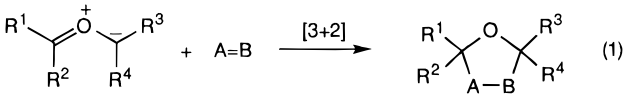
Ethyl diazoacetate undergoes dirhodium(II)-catalyzed reactions with aryl aldehydes to form 1,3-dioxolanes as mixtures of diastereoisomers in good yields. Carbonyl ylides are reaction intermediates. Catalyst dependent diastereocontrol is observed for reactions with *p*-nitrobenzaldehyde, but not for those with *p*-anisaldehyde or benzaldehyde, so that at least with transformations involving *p*-nitrobenzaldehyde a metal-stabilized ylide is responsible for product formation. Higher yields are obtained with catalysis by dirhodium(II) carboxamidates than with the carboxylates. Diastereoselectivity in 1,3-dioxolane formation that occurs through the "free" ylide can be effectively controlled so that only one diastereomer is produced through the use of 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate (BDA) or dicyclohexylmethyl diazoacetate (DCM). The thermodynamically least stable all-cis trisubstituted 1,3-dioxolane is the primary product from *p*-nitrobenzaldehyde "cycloaddition" to the metal-stabilized ylide. Reactions that take place in the presence of *p*-anisaldehyde and dimethyl acetylenedicarboxylate (DMAD) result in the formation of one 2,5-dihydrofuran-2-carboxylate stereoisomer in good yield. In contrast, with *p*-nitrobenzaldehyde and DMAD both dihydrofuran stereoisomers are produced along with, mainly, the dioxolane derived from the metal-stabilized ylide; there is in this case competition between addition reactions of the "free" ylide and the metal-associated ylide.

The formation/reactions of carbonyl ylides continues to be a subject of considerable interest and intensive investigation.[1−3] Their usefulness as intermediates for heterocyclic syntheses stems from their reactivity toward a variety of dipolarophiles, including alkenes, alkynes, and aldehydes (eq 1). The catalytic generation of carbonyl ylides from diazo compounds,[2−5] especially in intramolecular reactions,[6,7] has significantly broadened their applicability for natural product synthesis.



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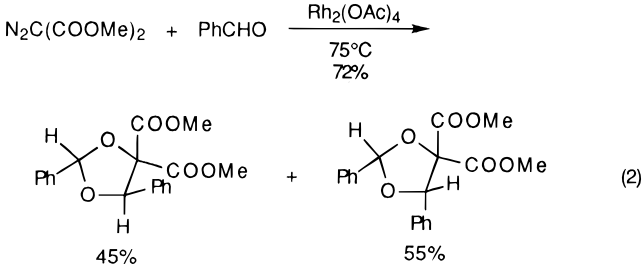
Intermolecular reactions emanating from transition metal catalyzed diazo decomposition in the presence of aldehydes or ketones have received limited attention. Early investigations by Huisgen and de March with dimethyl diazomalonate revealed that a mixture of two major dioxolane stereoisomers was formed in the Cu(acac)$_2$-, Rh$_2$(OAc)$_4$-, or Cu(OTf)-catalyzed reaction with benzaldehyde (eq 2),[8] and this transformation was confirmed with carbenes generated in the presence of aldehydes or ketones by noncatalytic methods.[9,10] Trapping of the initially-formed carbonyl ylide with dimethyl fumarate or dimethyl maleate occurred with greater efficiency to form the anticipated two-component product mixture (eq 3), but reactions with ethyl diazoacetate were limited because of pyrrazoline formation with the α,β-unsaturated diester dipolarophiles.[8b] Maas has recently



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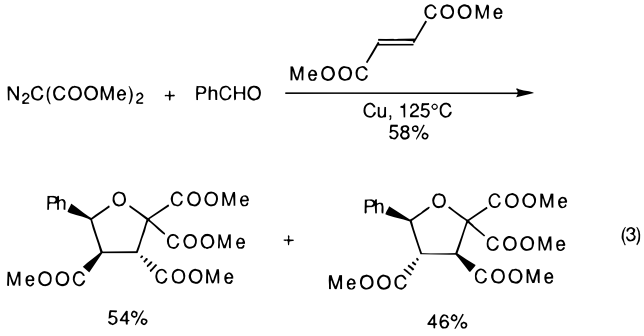

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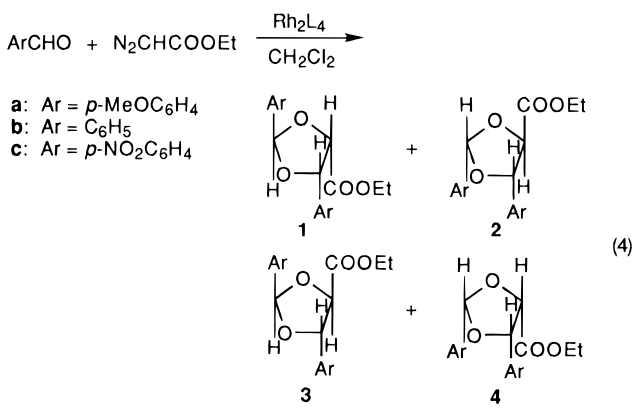
reported that the carbonyl ylide generated from diazo(trialkylsilyl)acetates can be successfully trapped with fumarate, maleate, or acetylenedicarboxylate in moderate yields using $Rh_2(pfb)_4$ (pfb = perfluorobutyrate) or $[Ru_2(CO)_4(OAc)_2]_n$.[11] Reactions with alkyl diazoacetates, from which as many as four isomeric dioxolanes could be formed, were originally reported by Dieckmann[12] and have been recently described in only two instances,[13,14] and in these cases the primary product(s) was not the dioxolane(s). We have investigated the dirhodium(II)-catalyzed reactions of diazoacetates with benzaldehydes and are now able to report the dominant factors for product stereocontrol and the reagents suitable to achieve the formation of only one diastereoisomer.

Results and Discussion

Treatment of a composite of *p*-anisaldehyde and a catalytic amount of $Rh_2(OAc)_4$ in anhydrous CH_2Cl_2 with ethyl diazoacetate resulted in the formation of two carbonyl ylide cycloaddition products, identified as **1** and **2** out of the four possible diastereomers (eq 4, Ar = *p*-$MeOC_6H_4$), in less than 15% yield. Higher conversions



(4)

were achieved with catalysis by dirhodium(II) caprolactamate, $Rh_2(cap)_4$ (52% yield) and, optimally, with dirhodium(II) tetrakis[methyl 2-oxapyrrolidine-5(*S*)-carboxylate], $Rh_2(5S\text{-MEPY})_4$ (77% yield), but the ratio of **1:2** did not change from 52:48. Isomers **3** and **4** were not detected in the isolated product mixture, and if formed, they were present in a combined relative yield of less than 5%. Product stereochemistry for **1** and **2** was determined by 2D and NOE experiments and their characteristic H4−H5 NMR vicinal coupling constants (J = 7.2 Hz for **1**; J = 6.2 Hz for **2**). Benzaldehyde yielded similar products (**1b** and **2b**) in the same isomer ratio (52:48) when reacted with ethyl diazoacetate in the presence of $Rh_2(cap)_4$, but isolated product yields were lower (27%); product yields increased to 39% with the use of $Rh_2(5S\text{-MEPY})_4$, but once again, the product ratio was the same. A minor 1,3-dioxolane product, less than one-fifth the amount of either **1b** or **2b**, was also obtained, and this compound was assigned to be isomer **4b** based on its ^1H NMR chemical shifts and coupling constants (J = 7.9 Hz for H4−H5) with correlation to the stereochemically well defined **4c** (Table 1). The amount of **4b** was as low as 6% (relative yield) from reactions catalyzed by $Rh_2(5S\text{-MEPY})_4$ and as high as 9% with $Rh_2(OAc)_4$; isomer **3b** was not detected. The only major competing reaction was carbene dimer formation.

Table 1. Characteristic NMR Chemical Shifts and Coupling Constants for 1−4

	δ, ppm				
compound	H2	H4	H5	CH_3	$J_{4,5}$, Hz
1a	6.69	5.42	4.92	0.88	7.2
1b	6.75	5.46	4.96	0.82	7.1
1c	6.83	5.51	5.05	0.88	7.2
2a	6.11	5.13	4.47	1.31	6.3
2b	6.19	5.22	4.53	1.34	6.1
2c	6.29	5.38	4.54	1.39	5.9
3c	6.39	5.39	4.62	1.31	6.0
4b	6.23	5.44	4.88	0.80	7.9
4c	6.19	5.61	5.02	0.86	7.9

Table 2. Influence of Catalyst on Product Stereochemistry for Reactions of *p*-Nitrobenzaldehyde with Ethyl Diazoacetate[a]

		relative yield, %			
catalyst	product yield, %[b]	**1c**	**2c**	**3c**	**4c**
$Cu(CH_3CN)_4PF_6$	39	11	9	10	70
$Rh_2(OAc)_4$	37	21	22	3	54
$Rh_2(OAc)_4$[c]	(30)[d]	9	9	t[e]	82
$Rh_2(pfb)_4$	41	28	20	7	45
$Rh_2(cap)_4$	35	43	41		16

[a] Reactions were performed with a 3-fold molar excess of *p*-nitrobenzaldehyde. [b] Yield after chromatographic purification. [c] Reaction performed in the presence of a 3-fold molar excess of DMAD based on EDA. [d] Yield of both dioxolane and dihydrofuran products. [e] Trace amount.

With *p*-nitrobenzaldehyde all four 1,3-dioxolane products were observed (**1c:2c:3c:4c** = 21:22:3:54) from reactions catalyzed by $Rh_2(OAc)_4$ (37% yield), and surprisingly, the major isomer was the all-cis **4c**. The stereochemistry of **4c** was established by NOE experiments, and the H4−H5 vicinal coupling constant for this isomer was 7.9 Hz. The structures of isomers **1c** and **2c** were determined from their characteristic chemical shifts and coupling constants (Table 1). Unlike reactions with *p*-anisaldehyde and benzaldehyde, however, where catalyst influence on product selectivity was not observed, when reactions between ethyl diazoacetate and *p*-nitrobenzaldehyde were performed in the presence of different catalysts, the product isomer ratio changed from predominantly **4c** with $Cu(CH_3CN)_4PF_6$ and $Rh_2(OAc)_4$ to predominantly **1c** + **2c** with $Rh_2(cap)_4$ and $Rh_2(5S\text{-MEPY})_4$ (Table 2). The **1c:2c** product ratio did not change through this series of catalysts, but those for **4c:3c** and (**1** + **2**)/(**3** + **4**) changed dramatically. This strong influence of catalyst on product selectivity is unprecedented in carbonyl ylide chemistry[15] and requires that the catalyst remains associated with the ylide during cycloaddition.

Four dioxolane isomers **1**−**4** can arise from aldehyde cycloaddition to the four limiting carbonyl ylide isomers **5**−**8** (Scheme 1). The preferential formation of **1** and **2** with *p*-anisaldehyde and benzaldehyde corresponds to cycloaddition of **6** or **8**. Semiempirical calculations using the AM1 basis set suggest that **6** is of lower energy than **8** (4.4 kcal/mol) and, as expected, that **5** is of lower energy than **7**. In the series of *p*-anisaldehyde to *p*-nitrobenzaldehyde, **6** was lower in energy than either **5** (4.3 kcal/

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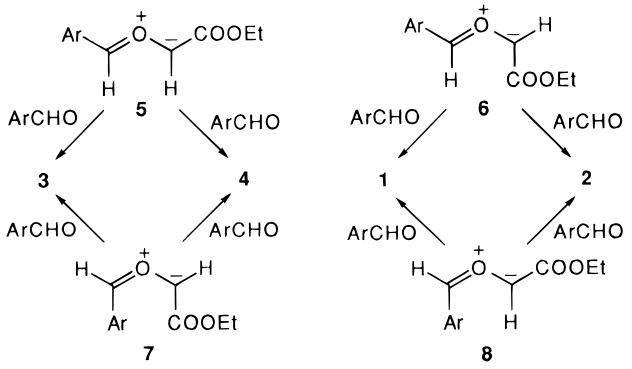
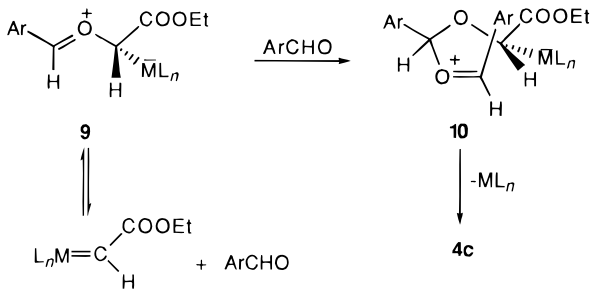
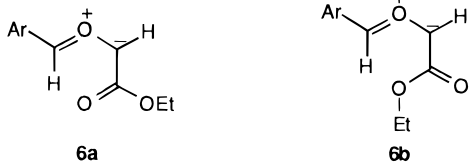
Scheme 1



Scheme 2

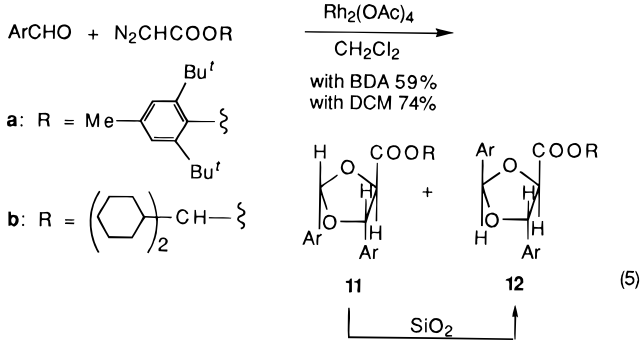


mol) or **8**, attesting to the relative freedom of **6a**, which is more stable (2.4 kcal/mol) than **6b**, from electronic



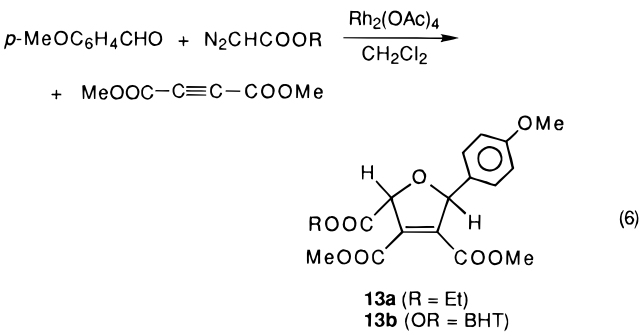
repulsions. The energy differences are small, but their trends are consistent with what is observed for reactions with *p*-anisaldehyde and benzaldehyde. The exception is *p*-nitrobenzaldehyde from which catalyst-dependent production of **4c** is important; the formation of this product can be assumed to involve the metal-associated ylide **9**, rather than **5**, and to occur through the pathway outlined in Scheme 2. Preference for **4c** rather than **3c** is probably due to the minimization of steric effects that for **10** allows Ar to avoid interaction with the protruding H on the carbenic carbon.

To reduce the number of products in reactions proceeding through the "free" ylide **6**, we reasoned that increasing the steric bulk of the ester would influence the orientation of the dipolarophile with respect to **6** and direct dipolar addition to form, prefentially, trans isomer **2**. Initial experiments with *tert*-butyl diazoacetate and *l*-menthyl diazoacetates suggested the feasibility of this approach, but only with 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate (BDA), which we previously introduced as an exceptionally selective diazoacetate in catalytic intermolecular cyclopropanation reactions,[16] and dicyclohexylmethyl diazoacetate (DCM), which had been used by Masamune,[17] were we able to achieve complete or nearly complete diastereocontrol (eq 5, Ar = *p*-$MeOC_6H_4$). Only



11b was formed in reactions with DCM (74% isolated yield), but with BDA a second minor product consistent with **12a** was also detected (**11a:12a** = 96:4). The assignment of the major isomer to **11** was based on its NMR chemical shift and coupling constant (J = 6.1−6.2 Hz) correlations with **2** and by NOE experiments. Isomer **12a** had a H4−H5 coupling constant of 5.6 Hz and was formed from **11a** by isomerization over silica gel. The use of BDA with *p*-nitrobenzaldehyde was not favorable toward product formation.

The three-component cyclization—from diazoacetate, aldehyde, and dimethyl acetylenedicarboxylate (DMAD)—was also successful. Treatment of EDA with 3-fold molar excesses of *p*-anisaldehyde and DMAD in the presence of $Rh_2(OAc)_4$ resulted in the formation of dihydrofuran **13a** in 51% isolated yield and, consistent with the dominant formation of ylide **6** (Scheme 1), solely as the trans stereoisomer (eq 6). The use of BDA resulted in



the formation of **13b** in 67% isolated yield. None of the *cis*-stereoisomer, which could have been formed by cycloaddition to either **5** or **7**, was observed. Attempts to cause asymmetric induction in **13a** using chiral dirhodium(II) catalysts were not successful (<10% ee).

When *p*-nitrobenzaldehyde was used in place of *p*-anisaldehyde, with EDA and DMAD as coreactants and $Rh_2(OAc)_4$ as the catalyst, the full complement of products was obtained: both *cis*- and *trans*-2,5-disubstituted dihydrofuran isomers, **14c** and **14t**, and dioxolanes **1c**−**4c** (eq 7). However, the all-cis **4c** was, by far, the major dioxolane product (82% of total, Table 2). Given that dihydrofuran **14t** and dioxolane **1c** + **2c** are derived from **6** whereas **14c** and **3c** + **4c** result from reactions of **5** and/or **9**, the consequent ratio of products [(**14t** + **1c** + **2c**)/(**14c** + **3c** + **4c**)] is 35:65, which is virtually identical with the 40:60 ratio of products formed in the absence of DMAD. That this ratio does not change, even as the use of DMAD appears to drain ylide intermediates that produce **1c** and **2c**, suggests that a rapid equilibrium controls access to these stereoisomeric products. Also, since **6** is of lower energy than **5**, this data shows that there is no interconversion between **5**, if formed, and **6**.

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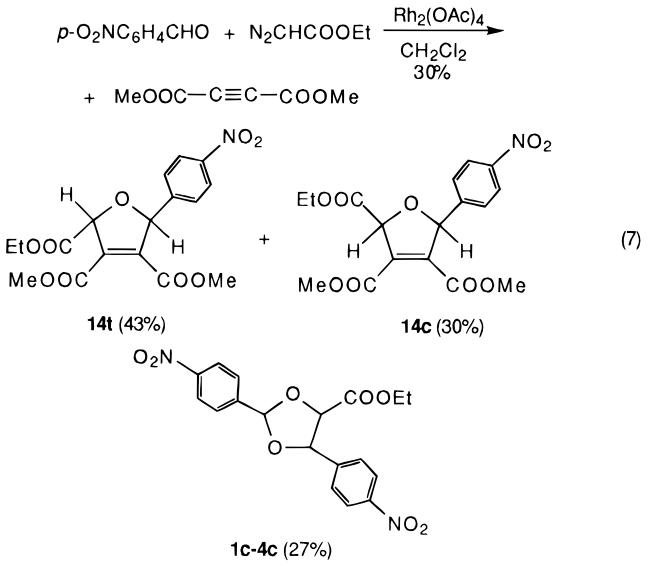


(7)

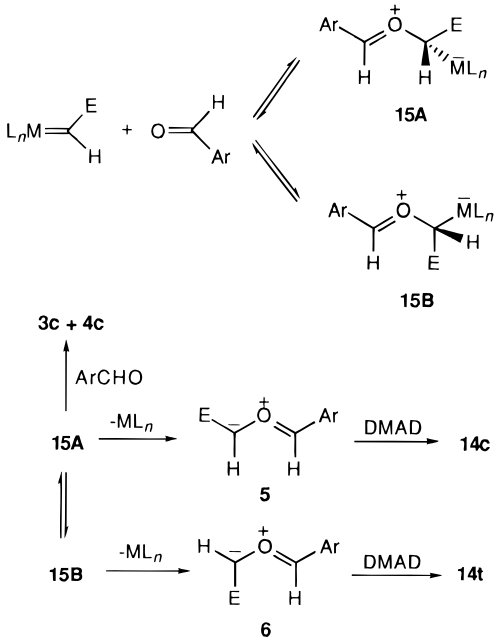
A mechanism which accounts for the results of eqs 6 and 7 is that shown in Scheme 3. Initial addition of the nucleophilic aldehyde to the electrophilic metal carbene forms metal-stabilized ylides **15A** and **15B** which are conformational isomers and interconvertible either by rotation or by dissociation−recombination. Dissociation of the ligated metal forms either **5** or **6** from which **14c** or **14t**, respectively, are formed by cycloaddition with DMAD. Dioxolanes **3c** and **4c** are formed from the metal-stabilized ylide **15A** in competition with dissociation of the ligated metal as a result of a stereoelectronic barrier to metal−carbon bond cleavage. In accord with this interpretation, doubling the concentration of *p*-nitrobenzaldehyde increases the ratio of dioxolane to dihydrofuran products from 27:73 (eq 7) to 45:55 without changing either the **14c**:**14t** or **1c:2c:3c:4c** ratios. The residual **1c** + **2c** formed with *p*-nitrobenzaldehyde may be derived from **15B** rather than **6**. As suggested from results with *p*-anisaldehyde, there is a >50:1 preference in reactivity for cycloaddition of **6** with DMAD relative to aldehyde.

Summary. The results obtained for catalyst-derived carbonyl ylide formation show that there is a dual pathway to cycloaddition products. Stereoelectronic factors control "free" ylide formation so that **6** is the sole ylide product from reactions with *p*-anisaldehyde; stereoselectivity for cycloaddition is controlled by steric effects. Metal-stabilized carbonyl ylides can undergo stepwise addition of a carbonyl group to produce dioxolane products not observed from the "free" ylide, and steric effects inherent in the addition process provide significant stereocontrol. This interpretation suggests that prior observations of catalyst-dependent selectivity in ylide transformations of diazocarbonyl compounds[18] may, in fact, be the result of reactions with metal-stabilized ylides and should be revisited.

Experimental Section

General. ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were obtained as solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm, δ) downfield from internal Me_4Si (TMS). Mass spectra were obtained using electron ionization (70 eV) on a quadrupole instrument. Infrared spectra were recorded as a thin film on sodium chloride plates or in a KBr pellet as indicated, and absorptions are reported in wavenumbers (cm^{-1}). Melting points are uncorrected. Elemental analyses were performed at Texas Analytical Laboratories, Inc. Anhydrous CH_2Cl_2 was dried over calcium hydride for 24 h and then distilled prior to use in catalytic reactions. BDA[16] and DCM[17] were prepared as previously described. Dirhodium(II) catalysts were prepared by standard methods: $Rh_2(pfb)_4$,[19] $Rh_2(cap)_4$,[20] $Rh_2(5S\text{-}MEPY)_4$;[21] $Rh_2(OAc)_4$ was recrystallized from methanol prior to use. The $Cu(MeCN)_4PF_6$ catalyst was prepared according to the literature procedure.[22]

Scheme 3



Reaction of *p*-Anisaldehyde with Ethyl Diazoacetate. To a solution of *p*-anisaldehyde (1.36 g, 10.0 mmol) and $Rh_2(cap)_4$ (20 mg, 0.031 mmol) in 5.0 mL of refluxing anhydrous CH_2Cl_2 was added a solution of ethyl diazoacetate (0.342 g, 3.00 mmol) in 10 mL of CH_2Cl_2 at a rate of 1.7 mL/h. After the addition was complete, the light green reaction solution was cooled to room temperature and then filtered through a short plug of silica to remove the catalyst, and the silica plug was washed with 20 mL of CH_2Cl_2. The solvent was evaporated under reduced pressure, and excess aldehyde was vacuum distilled. The residue was subjected to GC and NMR analyses and then purified by chromatography on silica (hexanes:EtOAc, 4:1 → 1:1) to give 1,3-dioxolanes **1a** and **2a** (0.58 g, 1.56 mmol, 52% yield). For **1a**: ^{1}H NMR δ 7.47 (d, J = 8.3 Hz, 2 H), 7.30 (d, J = 8.3 Hz, 2 H), 6.92 (d, J = 8.3 Hz, 2 H), 6.86 (d, J = 8.3 Hz, 2 H), 6.69 (s, 1 H), 5.42 (d, J = 7.2 Hz, 1 H), 4.92 (d, J = 7.2 Hz, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.90−3.63 (comp, 2 H), 0.88 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 171.0, 160.3, 159.8, 130.7, 128.5, 128.3, 127.9, 127.7, 114.1, 113.9, 105.4, 79.6, 79.2, 61.6, 55.4, 14.3; mass spectrum, *m*/*z* (relative abundance) 194 (3), 166 (12), 165 (100), 149 (39), 148 (35), 137 (42), 135 (58), 121 (53), 91 (26), 77 (36); NOE enhancement (H2−H4−H5) and COSY experiments established cis geometry for ^{1}H NMR absorptions at δ 5.42 and 4.92 and anti relationship to absorption at δ 6.69. For **2a**: ^{1}H NMR δ 7.53 (d, J = 8.8 Hz, 2 H), 7.40 (d, J = 8.8 Hz, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 6.92 (d, J = 8.8 Hz, 2 H), 6.11 (s, 1 H), 5.13 (d, J = 6.3 Hz, 1 H), 4.47 (d, J = 6.3 Hz, 1 H), 4.37−4.23 (comp,

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2 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 1.31 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 169.3, 160.8, 159.9, 131.1, 128.5, 128.0, 127.9, 127.6, 113.9, 113.7, 105.4, 82.0, 81.0, 60.9, 55.4, 13.7; mass spectrum, m/z (relative abundance) 194 (2), 166 (12), 165 (100), 149 (48), 148 (35), 137 (40), 135 (75), 121 (60), 91 (28), 77 (39); NOE enhancement and COSY experiments establish trans geometry for ^{1}H NMR absorptions at δ 5.13 and 4.47 and syn relationship between absorptions at δ 5.13 and 6.11. Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 66.91; H, 6.22.

Reaction of Benzaldehyde with Ethyl Diazoacetate. Ethyl diazoacetate (0.114 g, 1.00 mmol) in 5.0 mL of anhydrous CH_2Cl_2 was added by syringe pump over 12 h to a refluxing solution of benzaldehyde (0.318 g, 3.00 mmol) and Rh_2(5*S*-MEPY)$_4$ (8.6 mg, 10 mmol) in 5.0 mL of CH_2Cl_2. After addition was complete, the reaction mixture was treated as previously described. Benzaldehyde was removed by bulb-to-bulb distillation under vacuum (0.135 g recovery), and the residue was purified by flash chromatography on silica (9:1 hexanes:ethyl acetate) to give a white solid as a mixture of three 1,3-dioxolane isomers (0.16 g, 0.389 mmol, 39% yield). For **1b**: ^{1}H NMR δ 7.67−7.24 (m, 10 H), 6.75 (s, 1 H), 5.46 (d, J = 7.1 Hz, 1 H), 4.96 (d, J = 7.1 Hz, 1 H), 3.85−3.76 (m, 1 H), 3.70−3.58 (m, 1 H), 0.82 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 170.8, 138.4, 135.9, 133.4, 129.8, 128.7, 128.4, 127.0, 126.1, 105.5, 79.9, 79.2, 61.6, 14.2; mass spectrum, m/z (relative abundance) 192 (19, M − PhCHO), 176 (40), 148 (15), 136 (10), 135 (100), 131 (34), 119 (25), 107 (42), 105 (38), 91 (58), 90 (20), 89 (25), 79 (22), 77 (32). For **2b**: ^{1}H NMR δ 7.66−7.27 (m, 10 H), 6.19 (s, 1 H), 5.22 (d, J = 6.1 Hz, 1 H), 4.53 (d, J = 6.1 Hz, 1 H), 4.37−4.25 (m, 2 H), 1.34 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 169.0, 138.1, 135.7, 133.5, 129.2, 128.5, 128.2, 126.6, 126.4, 105.5, 82.1, 81.1, 60.9, 13.5; mass spectrum, m/z (relative abundance) 192 (32, M − PhCHO), 176 (51), 148 (21), 136 (11), 135 (100) , 131 (49), 119 (50), 107 (46), 105 (87), 91 (91), 90 (31), 89 (38), 79 (26), 77 (51). Assignments of **1b** and **2b** were made by direct analogy to those from reaction with *p*-anisaldehyde (Table 1). For **4b**: ^{1}H NMR δ 7.66−7.25 (m, 10 H), 6.23 (s, 1 H), 5.44 (d, J = 7.9 Hz, 1 H), 4.88 (d, J = 7.9 Hz, 1 H), 3.83−3.72 (m, 1 H), 3.65−3.53 (m, 1 H), 0.80 (t, J = 7.2 Hz, 3 H); mass spectrum, m/z (relative abundance) 192 (50, M − PhCHO), 176 (1), 148 (2), 136 (9), 135 (100), 131 (7), 119 (26), 107 (33), 105 (31), 91 (49), 90 (18), 89 (21), 79 (17), 77 (28). Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.39; H, 6.15.

Reactions of *p*-Nitrobenzaldehyde with Ethyl Diazoacetate. Addition was performed as previously described using 3.0 molar equiv of *p*-nitrobenzaldehyde and 1.0 mol % of Rh_2(cap)$_4$ or Rh_2(OAc)$_4$. Analysis of the crude product mixture from the Rh_2(OAc)$_4$-catalyzed reaction by GC showed four distinct 1,3-dioxolanes in a ratio of 57:19:3:21; GC/MS analysis of these compounds demonstrated that they were diastereoisomers. Chromatographic separation of the dioxolane products from the reactant aldehyde on silica (6:1 hexanes:ethyl acetate) afforded the composite **1c**−**4c** in 35% yield (from Rh_2(cap)$_4$) and in 37% yield (from Rh_2(OAc)$_4$). Selective crystallization from 1:1 EtOAc:hexanes provided a pure sample of the major product (**4c**): mp 121−123 °C; ^{1}H NMR δ 8.34 (d, J = 8.7 Hz, 2 H), 8.23 (d, J = 8.7 Hz, 2 H), 7.99 (d, J = 8.7 Hz, 2 H), 7.56 (d, J = 8.7 Hz, 2 H), 6.19 (s, 1 H), 5.61 (d, J = 7.9 Hz, 1 H), 5.02 (d, J = 7.9 Hz, 1 H), 3.81 (dq, J = 10.9, 7.1 Hz, 1 H), 3.65 (dq, J= 10.9, 7.1 Hz, 1 H), 0.86 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 167.9, 148.9, 148.1, 142.2, 141.5, 128.5, 127.7, 123.7, 123.4, 103.9, 80.7, 78.6, 61.3, 13.6; mass spectrum, m/z (relative abundance) 194 (2), 193 (6), 181 (12), 180 (100), 164 (19), 149 (23), 135 (20), 118 (78), 105 (21), 90 (21), 89 (49), 78 (24), 77 (25); TLC R_f 0.42 (1:1 hexanes: EtOAc); NOE experiments established the stereochemistry of this product through correlations with ^{1}H NMR absorptions at δ 6.19, 5.61, and 5.02. For **1c**: ^{1}H NMR δ 8.29 (d, J = 8.7 Hz, 2 H), 8.24 (d, J = 8.7 Hz, 2 H), 7.74 (d, J = 8.7 Hz, 2 H), 7.59 (d, J = 8.7 Hz, 2 H), 6.83 (s, 1 H), 5.51 (d, J = 7.2 Hz, 1 H), 5.05 (d, J = 7.2 Hz, 1 H), 3.92−3.82 (m, 1 H), 3.75−3.64 (m, 1 H), 0.88 (t, J = 7.2 Hz, 3 H); mass spectrum, m/z (relative abundance) 194 (9), 193 (62), 181 (9), 180 (84), 176 (48), 164 (24), 152 (91), 150 (71), 149 (8), 147 (26), 135 (22), 118 (100), 105 (28), 90 (32), 89 (71), 78 (34), 77 (39). For **2c**: ^{1}H NMR δ 8.32 (d, J = 8.8 Hz, 2 H), 8.27 (d, J = 8.27 Hz, 2 H), 7.79 (d, J = 8.8 Hz, 2 H), 7.62 (d, J = 8.8 Hz, 2 H), 6.29 (s, 1 H), 5.38 (d, J = 5.9 Hz, 1 H), 4.54 (d, J = 5.9 Hz, 1 H), 4.33−4.17 (comp, 2 H), 1.39 (t, J = 7.2 Hz, 3 H); mass spectrum, m/z (relative abundance) 194 (7), 193 (46), 181 (11), 180 (96), 176 (34), 164 (13), 152 (100), 150 (32), 147 (18), 135 (11), 118 (66), 105 (21), 90 (25), 89 (55), 78 (28), 77 (27). For **3c** only the distinguishing ^{1}H NMR absorptions (Table 1) could be discerned from product mixtures as this isomer proved to be resistant to purification: mass spectrum, m/z (relative abundance) 193 (18), 181 (9), 180 (72), 176 (18), 164 (24), 152 (79), 150 (47), 147 (26), 135 (15), 118 (100), 105 (27), 90 (28), 89 (59), 78 (36), 77 (33). Anal. Calcd for $C_{18}H_{15}N_2O_8$: C, 55.82; H, 3.90; N, 7.23. Found: C, 55.73; H, 3.86; N, 7.11.

Reaction of *p*-Anisaldehyde with 2,6-Di-*tert*-butyl-4-methylphenyl Diazoacetate. Following the standard procedure with *p*-anisaldehyde (415 mg, 3.06 mmol) and 1.0 mol % Rh_2(OAc)$_4$, use of BDA (248 mg, 0.867 mmol) added in 5.0 mL of CH_2Cl_2 over a 6-h period produced a dark brown viscous oil after filtration and removal of solvent and excess aldehyde. Purification by column chromatography on silica (4:1 hexanes: EtOAc) afforded, after evaporation of the solvent, 272 mg of a white solid identified as **11a** (59% yield): mp 50−51 °C; ^{1}H NMR δ 7.56 (d, J = 8.8 Hz, 2 H), 7.48 (d, J = 8.8 Hz, 2 H), 7.14 (d, J = 2.2 Hz, 1 H), 7.12 (d, J = 2.2 Hz, 1 H), 6.96 (d, J = 8.8 Hz, 2 H), 6.93 (d, J = 8.8 Hz, 2 H), 6.24 (s, 1 H), 5.57 (d, J = 6.2 Hz, 1 H), 4.79 (d, J = 6.2 Hz, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 2.32 (s, 3 H), 1.38 (s, 9 H), 1.28 (s, 9 H); ^{13}C NMR δ 171.2, 160.8, 159.9, 145.7, 142.0, 141.8, 134.9$_5$, 134.9$_4$, 129.9, 128.4, 128.3, 128.2, 127.1, 114.1, 113.8, 105.3, 82.0, 80.8, 55.3$_2$, 55.3$_0$, 35.3, 35.2, 31.6, 31.5, 21.5; IR (KBr) 3005, 2966, 2939, 2913, 2875, 2839, 1750, 1615, 1516 cm^{-1}; TLC R_f 0.42 (4:1 hexanes:EtOAc); NOE experiments (H2−H4−H5) established the product stereochemistry. Anal. Calcd for $C_{33}H_{40}O_6$: C, 74.41; H, 7.57. Found: C, 74.36; H, 7.56.

A second product, identified as **12a**, was observed following chromatographic purification, the **12a**:**11a** ratio being 4:96: ^{1}H NMR δ 7.57 (d, J = 8.8 Hz, 2 H), 7.47 (d, J = 8.8 Hz, 2 H), 7.15 (d, J = 2.1 Hz, 1 H), 7.13 (d, J = 2.1 Hz, 1 H), 7.01 (d, J = 8.8 H, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 6.23 (s, 1 H), 5.66 (d, J = 5.5 Hz, 1 H), 4.95 (d, J = 5.5 Hz, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 2.33 (s, 3 H), 1.35 (s, 9 H), 1.29 (s, 9 H). Addition of silica to the $CDCl_3$ solution of 96:4 **11a:12a** caused the slow conversion of **11a** to **12a** (**11a:12a** = 89:11 after 5 h, 82:18 after 19 h, and 76:24 after 50 h with no further change to 98 h).

Reaction of *p*-Anisaldehyde with Dicyclohexylmethyl Diazoacetate. To a solution of *p*-anisaldehyde (408 mg, 3.00 mmol) and Rh_2(OAc)$_4$ (2.2 mg, 5.0 μmol) in 5.0 mL of refluxing anhydrous CH_2Cl_2 was added a solution of dicyclohexylmethyl diazoacetate (132 mg, 0.500 mmol) in 5.0 mL of CH_2Cl_2 at a rate of 0.83 mL/h. After addition was complete, the reaction solution was filtered through a short plug of silica gel which was washed with 20 mL of CH_2Cl_2. The solvent was removed under reduced pressure, and excess aldehyde was vacuum distilled (372 mg recovered). Column chromatography of the viscous dark brown residue on silica (4:1 hexanes:EtOAc) afforded 187 mg of a colorless oil identified as **11b** (74% yield). Attempts to crystallize this compound were not successful: ^{1}H NMR δ 7.54 (d, J = 8.8 Hz, 2 H), 7.42 (d, J = 8.6 Hz, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 6.93 (d, J = 8.6 Hz, 2 H), 6.15 (s, 1 H), 5.19 (d, J = 6.1 Hz, 1 H), 4.77 (d, J = 5.4 Hz, 1 H), 4.54 (d, J = 6.1 Hz, 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 1.80−1.50 (m, 10 H), 1.30−0.85 (m, 10 H); ^{13}C NMR δ 171.0, 160.7, 159.9, 130.0, 128.4, 128.3, 128.1, 127.8, 114.0, 113.8, 113.6, 105.4, 82.8, 82.1, 81.1, 55.3, 38.3, 38.2, 29.9, 29.8, 27.6, 27.3, 26.3, 26.1, 26.1, 25.9, 25.9; IR (KBr) 2933, 2855, 1740 cm^{-1}; TLC R_f 0.37 (4:1 hexanes: EtOAc). Anal. Calcd for $C_{31}H_{40}O_6$: C, 73.21; H, 7.93. Found: C, 73.24; H, 7.86.

Reaction of *p*-Anisaldehyde with Ethyl Diazoacetate in the Presence of DMAD. Ethyl diazoacetate (114 mg, 1.00 mmol) in 5.0 mL of anhydrous CH_2Cl_2 was added via syringe pump over 6 h to a solution of DMAD (426 mg, 3.00 mmol), *p*-anisaldehyde (408 mg, 3.00 mmol), and Rh_2(OAc)$_4$ (4.4 mg, 1.0 mmol) at room temperature in 5 mL of CH_2Cl_2. After addition was complete, the reaction solution was passed

through a short plug of silica, and the silica plug was washed with an additional 20 mL of CH_2Cl_2. The crude reaction mixture was subjected to GC and ^{1}H NMR analyses and then distilled to remove excess *p*-anisaldehyde and DMAD. Column chromatography of the residue on silica gel (2:1 hexanes:ethyl acetate) afforded 199 mg of a light yellow oil (51% yield) identified as **ethyl 3,4-dicarbomethoxy-5-(*p*-methoxyphenyl)-2,5-dihydrofuran-2-carboxylate (13a)**: ^{1}H NMR δ 7.25 (d, J = 8.8 Hz, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 6.22 (d, J = 6.0 Hz, 1 H), 5.69 (d, J = 6.0 Hz, 1 H), 4.33−4.20 (comp, 2 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.64 (s, 3 H), 1.29 (t, J = 7.1 Hz, 3 H); ^{13}C NMR 168.5, 162.0, 161.9, 160.0, 140.7, 134.0, 129.2, 128.5, 113.8, 89.3, 84.3, 61.7, 55.0, 52.4, 52.2, 13.9; IR (film) 2984, 2956, 2907, 2841, 1743, 1669, 1612, 1250, 1031, 835, 733 cm^{-1}; TLC R_f 0.42 (1:1 hexanes:EtOAc). Anal. Calcd for $C_{18}H_{20}O_8$: C, 59.34; H, 5.53. Found: C, 59.30; H, 5.47.

Reaction of *p*-Anisaldehyde with 2,6-Di-*tert*-butyl-4-methylphenyl Diazoacetate in the Presence of DMAD. BDA (286 mg, 1.00 mmol) in 5.0 mL of anhydrous CH_2Cl_2 was added via syringe pump over 6 h to a solution of DMAD (432 mg, 3.04 mmol), *p*-anisaldehyde (413 mg, 3.04 mmol), and $Rh_2(OAc)_4$ (4.4 mg, 1.0 μmol) at room temperature in 5 mL of CH_2Cl_2. After addition was complete, the reaction solution was filtered through a short plug of silica which was washed with CH_2Cl_2. The excess aldehyde and DMAD were distilled under vacuum to leave a yellow solid residue which was purified by column chromatography on silica (9:1 hexanes:ethyl acetate) to give 360 mg of a white solid (67% yield) identified as **2,6-di-*tert*-butyl-4-methylphenyl 3,4-dicarbomethoxy-5-(*p*-methoxyphenyl)-2,5-dihydrofuran-2-carboxylate (13b):** mp 59−61 °C; ^{1}H NMR δ 7.30 (d, J = 8.8 Hz, 2 H), 7.12 (s, 2 H), 6.91 (d, J = 8.8 Hz, 2 H), 6.26 (d, J = 5.7 Hz, 1 H), 6.01 (d, J = 5.7 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.68 (s, 3 H), 2.31 (s, 3 H), 1.33_2 (s, 9 H), 132_7 (s, 9 H); ^{13}C NMR δ 169.0, 162.3, 161.5, 160.3, 145.7, 142.6, 141.9_4, 141.9_2, 135.0, 132.7, 129.0, 128.8, 127.2, 127.0, 114.1, 89.6, 85.5, 55.2, 52.5, 35.2, 31.5, 31.3, 21.4; IR (KBr) 3005, 2958, 2914, 2875, 2840, 1748 (C═O), 1734 (C═O) cm^{-1}. Anal. Calcd for $C_{31}H_{38}O_8$: C, 69.13; H, 7.11. Found: C, 69.04; H, 7.03.

Reaction of *p*-Nitrobenzaldehyde with Ethyl Diazoacetate in the Presence of DMAD. The same procedure as with *p*-anisaldehyde was employed. After addition was complete the reaction mixture was passed through a short plug of silica and washed with an additional 60 mL of CH_2Cl_2. GC and ^{1}H NMR analyses were performed, and then excess *p*-nitrobenzaldehyde was removed by sublimation at 0.4 Torr (100 °C). Separation of the dioxolane byproducts from the dihydrofurans was achieved by recrystallization (1:1 hexanes:EtOAc, 8 mL) whereby the dioxolane **4c** crystallized and dihydrofurans **14t** and **14c** remained in solution. Column chromatography of this residue on silica (1:1 hexanes:EtOAc) afforded 80 mg of a light yellow oil (30% yield) identified as **ethyl 3,4-dicarbomethoxy-5-(*p*-nitrophenyl)-2,5-dihydrofuran-2-carboxylate (14)**: bp 190 °C (0.03 Torr). For the trans isomer (**14t**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, J = 8.6 Hz, 2 H), 7.54 (d, J = 8.6 Hz, 2 H), 6.36 (d, J = 6.0 Hz, 1 H), 5.78 (d, J = 6.0 Hz, 1 H), 4.30 (q, J = 7.1 Hz, 2 H), 3.87 (s, 3 H), 3.67 (s, 3 H), 1.32 (t, J = 7.1 Hz, 3 H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.9, 161.6, 148.1, 144.5, 138.4, 136.0, 128.1, 123.5, 88.3, 84.9, 62.1, 52.7, 52.6, 13.9. For the cis isomer (**14c**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, J = 8.7 Hz, 2 H), 7.77 (d, J = 8.7 Hz, 2 H), 6.19 (d, J = 4.4 Hz, 1 H), 5.60 (d, J = 4.4 Hz, 1 H), 4.36−4.23 (comp, 2 H), 3.86 (s, 3 H), 3.75 (s, 3 H), 1.32 (*t*, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.9, 161.3, 148.1, 144.5, 138.1, 135.7, 128.8, 123.7, 88.5, 85.1, 62.1, 52.7, 52.5, 13.9; NOE experiments (H2−H5) established the product stereochemistry: IR (film) 1735, 1612, 1520, 1351 cm^{-1}; TLC R_f 0.45 (1:1 hexanes:EtOAc). Anal. Calcd for $C_{17}H_{17}NO_9$: C, 53.84; H, 4.52; N, 3.72. Found: C, 53.91; H, 4.50; N, 3.68. With 6 molar equiv of *p*-nitrobenzaldehyde instead of three, furan + dioxolane products were isolated in 31% yield (62 mg) with a 55/45 ratio of furan to dioxolanes; dioxolane diastereoisomers were found in the **1c:2c:3c:4c** ratio of 11:11:t:78.

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