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Rh-Catalyzed Formation of Dioxolanes from α-Alkyl Diazoesters: Diastereoselective Cycloadditions of Carbonyl Ylides with Selectivity over β-Hydride Elimination

Andrew DeAngelis, Patricia Panne, Glenn P. A. Yap, and Joseph M. Fox*

Brown Laboratories, Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

jmfox@udel.edu

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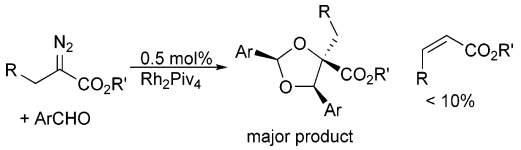
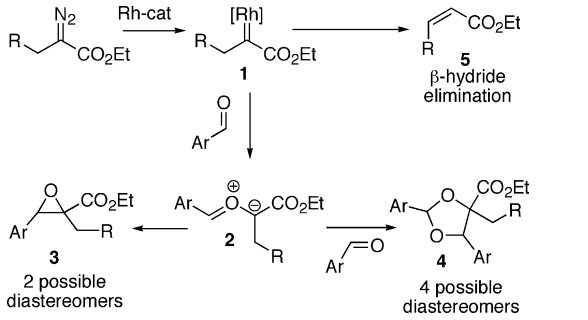


Described here is a diastereoselective Rh-catalyzed method for the preparation of dioxolanes from α-alkyl-α-diazoesters. This represents the first general method for generating carbonyl ylides from α-diazoesters that possess β-hydrogens, as such diazo compounds typically give rise to alkenes via β-hydride elimination. Subsequent cycloaddition with aromatic aldehydes gives tetrasubstituted dioxolanes with unusually high diastereoselectivity. A model is set forth to explain the diastereoselectivity of the cycloaddition.

Introduction

The transition metal-catalyzed reaction of α-diazoesters with aldehydes is a well-established route to substituted 1,3-dioxolanes.[1,2] This 3-component transformation proceeds through a putative[3] carbonyl ylide intermediate, and is an attractive method for the rapid assembly of molecular complexity. However, realizing chemo- and diastereoselectivity is a challenge for intermolecular reactions of carbonyl ylides, as is illustrated for rhodium carbene **1** and carbonyl ylide **2** in Scheme 1. Thus, ylide **2** can cyclize to epoxides **3**[4] (two possible diastereomers)

SCHEME 1. Issues of Chemo- and Diastereoselectivity for Rh-Catalyzed Generation and Reactions of Carbonyl Ylides



or undergo [3+2]-cycloaddition with a second aldehyde equivalent to yield dioxolanes **4**[2] (four possible diastereomers). For α-alkyl diazoesters, the scenerio is further challenged by intramolecular β-hydride elimination to give alkenes (**5**)—a side reaction that often precludes intermolecular chemistry of rhodium carbenoids.[5] Navigating these divergent reaction pathways to selectively produce a single product has proven challenging.

Examples of highly diastereoselective transformations that produce 1,3-dioxolanes from aldehydes and diazoesters are unusual. Jiang and co-workers have observed that the $Rh_2(OAc)_4$-catalyzed reactions of aldehydes with methyl α-diaz-

(1) Reviews on carbonyl ylide cycloadditions: (a) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley: New York, 1998. (c) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765.

(2) (a) de March, P.; Huisgen, R. *J. Am. Chem. Soc.* **1982**, *104*, 4953. (b) Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210. (c) Russell, A. E.; Brekan, J.; Gronenberg, L.; Doyle, M. P. *J. Org. Chem.* **2004**, *69*, 5269. (d) Jiang, B.; Zhang, X.; Luo, Z. *Org. Lett.* **2002**, *4*, 2453. (e) Nair, V.; Mathai, S.; Mathew, S. C.; Rath, N. P. *Tetrahedron* **2005**, *61*, 2849. (f) Lu, C.-D.; Chen, Z.-Y.; Liu, H.; Hu, W.-H.; Mi, A.-Q. *Org. Lett.* **2004**, *6*, 3071. (g) Alt, M.; Mass, G. *Tetrahedron* **1994**, *50*, 7435. (h) Wenkert, E.; Khatuya, H. *Tetrahedron Lett.* **1999**, *40*, 5439. For an elegant approach to controlling diastereoselective reactions of carbonyl ylides with a pendant Co-cluster, see: (i) Skaggs, A. J.; Lin, E. Y.; Jamison, T. F. *Org. Lett.* **2002**, *4*, 2277.

(3) There is evidence that some carbonyl ylides may be associated to Rh-carbenes.[2b,12]

(4) (a) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 933. (b) Davies, H. M. L.; DeMesse, J. *Tetrahedron Lett.* **2001**, *42*, 6803.

(5) For the Rh-catalyzed preparation of (*Z*)-alkenes via β-hydride elimination, see: Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908 and references cited therein.

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otrifluoromethylacetate leads to only one diastereomer in a majority of the cases studied.[2d] Diastereoselectivity is much lower with other diazoesters, and in some cases all four of the possible dioxolane diastereomers are produced.[2] Even with diazomalonate, where only two diastereomers are possible, both diastereomers are usually[6] formed.

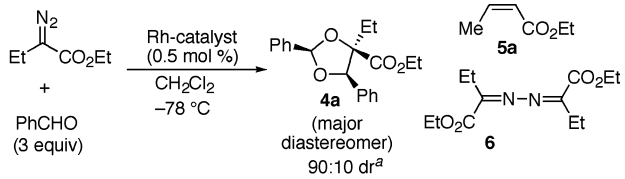
Padwa has elegantly demonstrated that intramolecular reactions between carbonyls and putative Rh-carbenes can produce carbonyl ylides with selectivity over β-hydride elimination.[7] However, no examples of intermolecular Rh-catalyzed reactions to form carbonyl ylides with selectivity over β-hydride elimination were known to us. Our group recently described conditions for two intermolecular Rh-catalyzed transformations of α-alkyl diazoesters that tolerate β-hydrogens: alkyne cyclopropenation and a tandem alkyne insertion/Büchner cascade to give dihydroazulenes.[8] Low reaction temperatures (−78 °C)[9] and the use of sterically demanding carboxylate ligands[10] [dirhodium tetrapivaloate (Rh_2Piv_4) or dirhodium tetra(triphenylacetate) (Rh_2TPA_4)] were key to the success of these reactions. In contrast, dirhodium tetraoctanoate (Rh_2Oct_4) led primarily to alkenes via β-hydride elimination.

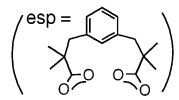
Described herein is a Rh-catalyzed method for generating putative carbonyl ylides from α-alkyl diazoesters with selectivity over β-hydride elimination. The putative carbonyl ylides are unusually reactive, and they combine with aromatic aldehydes at −78 °C to produce dioxolane products. Subsequent cycloaddition reactions with aromatic aldehydes proceed with excellent diastereoselectivity to give predominantly one dioxolane product.

Results and Discussion

A variety of rhodium(II) complexes were screened in the reaction of ethyl α-diazobutanoate with benzaldehyde (3 equiv) at −78 °C to form dioxolane **4a**. Competing reactions included β-hydrogen elimination to give *cis*-ethylcrotonate **5a** and the formation of azine **6**[11] as a single isomer (Table 1). Epoxides were not observed as side products. Rh_2Piv_4 was the most effective catalyst in terms of yield and selectivity (56% yield, 11:1 dioxolane/β-hydride elimination; Table 1, entry 4). While other carboxylate ligands were less effective than pivalate, the steric effect of the ligand was not as dramatic as was observed for cyclopropenation.[8] Thus, **4a** was still produced in 42% yield with Rh_2Oct_4—a catalyst that was completely ineffective for cyclopropenation. Temperature was a critical variable for achieving selective dioxolane formation. At −78 °C, the reactions are efficient. However, compound **4a** was formed only in low yield (11%) when the Rh_2Piv_4-catalyzed reaction of ethyl α-diazobutanoate with benzaldehyde was carried out at rt (Table 1, entry 5).

TABLE 1. Optimization of Conditions[d]



entry	catalyst	4a	5a	6
1	Rh_2OAc_4 (R = CH_3)	26%	18%	2%
2	Rh_2Oct_4 (R = C_7H_{15})	42%	5%	1%
3	Rh_2TPA_4 (R = CPh_3)	33%	9%	2%
4	Rh_2Piv_4 (R = CMe_3)	56%	5%	2%
5	Rh_2Piv_4 at r.t.	11%[c]	16%	1%
6	Rh_2TFA_4 (R = CF_3)	0%	87%	0%
7	Rh_2esp_2 (esp = )	44%	7%	5%
8	Rh_2(*S*-DOSP)$_4$[b]	23%	17%	1%
9	Rh_2(5*S*-MEPY)$_4$	0%	7%	44%

[a] Regardless of the catalyst that was employed, the same level of diastereoselectivity (±3%) was measured for all of the reactions studied at −78 °C. [b] Racemic **4a** was obtained from the reaction with Rh_2(*S*-DOSP)$_4$. [c] Determination of the dr by ^{1}H NMR analysis was prevented by an impurity with ^{1}H NMR resonances that overlapped with those of the minor diastereomer. [d] Ethyl α-diazobutanoate was added by syringe pump over a 3 h period. Yields and diastereomer ratios were determined by ^{1}H NMR analysis.

The selectivity of reactions of that involve carbonyl ylides can sometimes be altered by the nature of the Rh-catalyst, and in those cases it has been proposed that the cycloadditions involve metal-complexed dipoles.[2b,12] For the results presented in Table 1, it is proposed that the Rh-catalyst does not influence the final cycloaddition to form **4a**. Within the error of measurement by ^{1}H NMR integration (±3%), the same level of diastereoselectivity (90:10 dr) was observed for all of the reactions studied at −78 °C irrespective of the catalyst that was used. Davies' Rh_2(*S*-DOSP)$_4$ gave racemic **4a** in 23% yield and in 90:10 dr. The lack of catalyst influence on diastereoselectivity and the lack of asymmetric induction by the chiral catalyst support the hypothesis that the reaction to form **4a** involves the cycloaddition of a "free" ylide.

(6) The Rh_2OAc_4-catalyzed reaction of diazomalonate, phenanthrenequinone and aldehydes gives single diasteromers.[2e]

(7) (a) Padwa, A.; Zhang, Z. J.; Zhi, L. *J. Org. Chem.* **2000**, *65*, 5223. (b) Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem.* **1990**, *55*, 4144. (c) Padwa, A.; Herzog, D. L.; Chinn, R. L. *Tetrahedron Lett.* **1989**, *30*, 4077. (d) Padwa, A.; Deen, D. C.; Hertzog, D. L.; Nadler, W. R.; Zhi, L. *Tetrahedron* **1992**, *48*, 7565.

(8) (a) Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22. For other examples of Rh-catalyzed transformations that tolerate β-hydrogens, see refs 9 and 10.

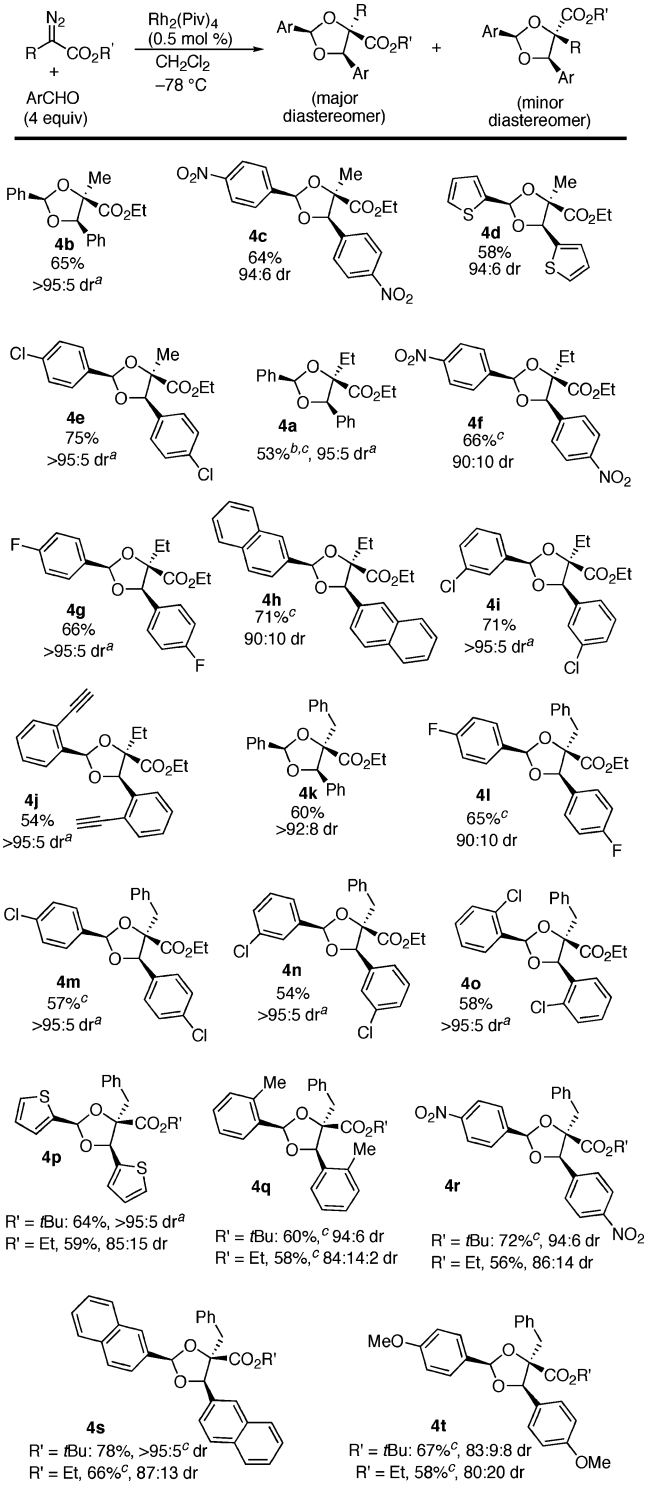
(9) Hashimoto and co-workers had noted in enantioselective, intramolecular C−H insertions that higher selectivities over β-hydride elimination were obtained at −78 °C: Minami, K.; Saito, H.; Tsutsui, H.; Nambu, H.; Anada, M.; Hashimoto, S. *Adv. Synth. Catal.* **2005**, *347*, 1483.

(10) For O−H insertion or intramolecular C−H insertions, modest improvements in selectivity over β-hydride elimination had been observed with $Rh_2(Piv)_4$ or Rh_2(9-adamantoate)$_4$: (a) Cox, G. G.; Haigh, D.; Hindley, R. M.; Miller, D. J.; Moody, C. J. *Tetrahedron Lett.* **1994**, *35*, 3139. (b) Taber, D. F.; Joshi, P. V. *J. Org. Chem.* **2004**, *69*, 4276. (c) Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992**, *57*, 436.

(11) The stereochemistry of **6** was not assigned. For precedent for the formation of azines in Rh-catalyzed reactions of diazocompounds, see ref 10c and: (a) Petrukhina, M. A.; Andreini, K. W.; Walji, A. M.; Davies, H. M. L. *J. Chem. Soc., Dalton Trans.* **2003**, 4221. (b) Ohno, M.; Itoh, M.; Umeda, M.; Furuta, R.; Kondo, K.; Eguchi, S. *J. Am. Chem. Soc.* **1996**, *118*, 7075. (c) Ace, K. W.; Husain, N.; Lathbury, D. C.; Morgan, D. *Tetrahedron Lett.* **1995**, *36*, 8141. (d) Pomerantz, M.; Levanon, M. *Tetrahedron Lett.* **1990**, *31*, 4265. (e) Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906.

(12) (a) Padwa, A. *J. Organomet. Chem.* **2005**, *690*, 5533. (b) Hodgson, D. M.; Stupple, P. A.; Pierard, F. Y. T. M.; Labande, A. H.; Johnstone, C. *Chem. Eur. J.* **2001**, *7*, 4465. (c) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50. (d) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (e) Kitigaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1999**, *121*, 1417.

TABLE 2. Chemoselective, Diastereoselective Dioxolane Synthesis[d]



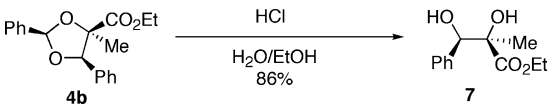
[a] The detection threshold for NMR analysis was considered to be 5%. [b] The isolated yield of **4a** was slightly lower than the yield measured by ^{1}H NMR shown in Table 1. The dr (95:5) measured for **4a** when 4 equiv of benzaldehyde was used (this table) was slightly higher than that measured when 3 equiv of benzaldehyde was used (Table 1). [c] Isolated as a mixture of two diastereomers. [d] Yields represent isolated yields (average of 2 runs) of the major diastereomer, unless noted otherwise. Diastereomer ratios were determined by ^{1}H NMR analysis.

Optimized conditions for dioxolane formation were applied to a variety of aldehydes, as shown in Table 2. Highest yields were obtained with 4 equiv of aldehyde; the yield was not improved significantly upon increasing to 5 equiv of aldehyde. Dioxolane formation is successful with α-diazopropionate, α-diazobutanoate, and α-diazohydrocinnamate. The success of α-diazohydrocinnimate is notable given the susceptiblility of benzylic hydrogens to undergo *β*-hydride elimination.

Dioxolane products were obtained in 53−78% yield. The method is broadly applicable to aromatic aldehydes. Functional groups that are tolerated on the benzaldehyde component include alkyl, alkoxy, halogen, nitro, and ethynyl groups. Ortho-substituted benzaldehydes, *β*-naphthaldehyde, and 2-thiophenecarboxaldehyde are also viable reaction partners. We also know of several limitations to the method described in Table 2: ethyl α-diazoisovalerate led only to ethyl 3-methylcrotonate—the product of *β*-hydride elimination. Complex mixtures were obtained in the reactions of ethyl α-diazopropionate with cinnamaldehyde, octanal, or acetaldehyde. The reaction of ethyl α-diazopropionate with *N*-lauroylindole-3-carboxaldehyde was also unsuccessful and led to a complex mixture.

For each reaction described in Table 2, the major product was assigned as the diastereomer with the aryl groups and the ester situated on the same face of the dioxolane ring; the minor diasteromer was assigned to have the opposite stereochemistry at C-4. For the syntheses of **4p**−**t**, the diastereomer ratios were less than 90:10 with ethyl α-diazohydrocinnamate. Previously, Doyle and co-workers demonstrated that sterically demanding esters gave improved diastereoselectivity in dioxolane formation from carbonyl ylides.[2b] Accordingly, we investigated the reactivity of *tert*-butyl α-diazohydrocinnamate. With this modification, it was possible to attain >90% diastereoselectivity for all but one of the entries (**4t**) in Table 2, and in the preparations of several derivatives [**4b**, **4e**, **4i**, **4p(tBu)**, and **4s(tBu)**] only the major diastereomer could be detected by ^{1}H NMR. Because 2-aryl-1,3-dioxolanes can be hydrolyzed, the described method constitutes a stereoselective synthesis of *vicinal* diols. Thus, dioxolane **4b** was converted to diol **7** in 86% yield under acidic conditions as shown in Scheme 2.

SCHEME 2. Acetal Hydrolysis Provides *Vicinal* Diols



Stereochemical assignments were made on the basis of ^{1}H NMR analysis and X-ray crystal structures for the major diastereomers of **4b**, **4k**, **4j**, **4o**, **4r** (R′ = Et), and **4s** (R′ = Et), and for the minor diastereomers of **4r** (R′ = Et) and **4s** (R′ = Et). A model that is consistent with the observed diastereoselectivity is proposed in Figure 1. The major product is proposed to arise from endo approach of the aldehyde to ylide conformer **A**, and the minor diastereomer from endo approach to conformer **B**.

The cycloadditions of carbonyl ylides to form dioxolanes are facile at −78 °C. To prove that the cycloaddition reactions were completed at −78 °C, and not while the reactions were being warmed to rt, the following experiment was conducted: 5 min after the addition of ethyl α-diazohydrocinnamate to the solution of Rh_2Piv_4/4-chlorobenzaldehyde (4 equiv) was completed, a cold (−78 °C) solution of 4-fluorobenzaldehyde (4 equiv) in CH_2Cl_2 was added. The mixture was then allowed to warm to rt. Analysis of the crude ^{1}H NMR indicated that **4m** was the only dioxolane product; ***4l*** was not detected, nor were "crossed" dioxolane products (Scheme 3). The experiment implies that the ylide had completely reacted prior to addition of 4-fluorobenzaldehyde.

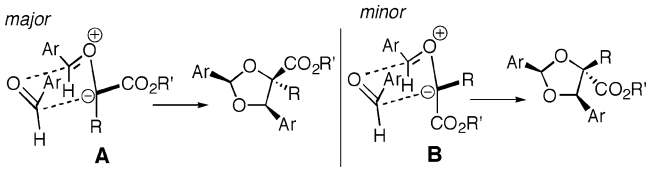
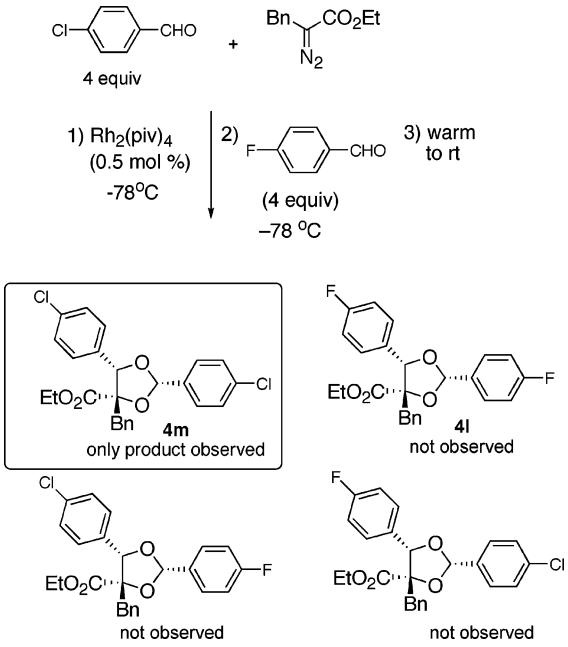


FIGURE 1. Proposed model to explain diastereoselectivity.

SCHEME 3. "Crossover" Experiment Demonstrates That the 1,3-Dipolar Cycloaddition Had Taken Place at −78 °C, and Not While the Reaction Warmed to Room Temperature



Carbonyl ylides derived from α-alkyl-α-diazoesters are unusual because they form and react productively at −78 °C. Under similar conditions (−78 °C) to those reported in Table 2, ethyl diazoacetate and benzaldehyde give only diethyl maleate and diethyl fumerate. The sense of diastereoselectivity is also unusual. Endo transition states via conformer **B** (Figure 1) have been proposed for the reactions of carbonyl ylides derived from methyl α-trimethylsilyl-α-diazoacetate,[2g] methyl α-trifluoromethyl-α-diazoacetate,[2d] and methyl α-phenyl-α-diazoacetate.[2f] The reason that the reactions of carbonyl ylides derived from α-alkyl-α-diazoesters apparently arise from conformer **A** may be related to steric considerations. An empirical observation from Table 2 is that the diastereoselectivity is highest when the alkyl substitutent is small and the ester substitutent is large. For example, the ethyl ester **4c** (R = Me) is produced with 94:6 dr, whereas the ethyl esters **4f** (R = Et) and **4r(Et)** (R = Bn) are produced in 90:10 and 86:14 dr, respectively. Thus, the increase in the size of the α-alkyl substitutent (Bn > Et > Me) is accompanied by a decrease in diastereoselectivity (Me > Et > Bn). This trend can be countered by increasing the size of the ester substitutent. Thus, *t*-Bu ester **4r(*t*-Bu)** (R = Bn) is formed with 94:6 dr. Therefore, these observations are consistent with prior observations in the literature that carbonyl ylides with relatively large α-alkyl substitutents (Ph,[2f] TMS,[2g] CF_3[2d]) are controlled by endo approach via conformer **B**.

In summary, general conditions are described for the Rh-catalyzed generation of carbonyl ylides from α-diazoesters that possess *β*-hydrogens. Subsequent cycloaddition with aromatic aldehydes gives tetrasubstituted dioxolanes with unusually high diastereoselectivity. Rh_2Piv_4 is the optimal catalyst for the transformations, and it is essential to carry out the reactions at low temperature (−78 °C) in order to achieve high yield and diastereoselectivity. A model is set forth to explain the diastereoselectivity of the cycloaddition based on an endo transition state.

Experimental Section

Representative Procedures for Dioxolane Formation: 2*β*,5*β*-Di(4-fluorophenyl)-4*β*-ethoxycarbonyl-4α-ethyl-1,3-dioxolane (4g). A dry round-bottomed flask was charged with $Rh_2(piv)_4$ (2 mg, 0.004 mmol) and the flask was evacuated and filled with nitrogen. Anhydrous CH_2Cl_2 (5 mL) and 4-fluorobenzaldehyde (332 mg, 2.68 mmol) were added, and the flask was cooled by a bath of dry ice/acetone. Ethyl 2-diazobutanoate (95 mg, 0.67 mmol) was dissolved in 3 mL of anhydrous CH_2Cl_2 and added to the reaction mixture via syringe pump at a rate of 1 mL/h. Following addition, the reaction mixture was allowed to warm to room temperature and mesitylene (80 mg, 0.67 mmol) was added. ^{1}H NMR analysis was then performed and the diastereomer ratio was determined to be >95:5. The solvent was then removed and the residue was chromatographed on silica gel with 1−5% ethyl acetate/hexanes as the eluent to give 168 mg (70%) of the title compound as a clear oil. A similar experiment gave the title compound in 61% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.85 (m, 2H), 7.35 (m, 2H), 7.14 (m, 2H), 7.03 (m, 2H), 6.13 (s, 1H), 4.99 (s, 1H), 3.77−3.88 (m, 1H), 3.52−3.62 (m, 1H), 2.20−2.31 (m, 1H), 1.88−2.01 (m, 1H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 170.5 (u), 163.9 (u) (d, ^1J(CF) = 246 Hz), 163.0 (u) (^1J(CF) = 246 Hz), 132.4 (u) (d, ^4J(CF) = 3 Hz), 131.2 (u) (d, ^4J(CF) = 3 Hz), 129.9 (dn) (d, ^3J(CF) = 8 Hz), 128.2 (dn) (d, ^3J(CF) = 8 Hz), 115.5 (dn) (d, ^2J(CF) = 21 Hz), 115.2 (dn) (d, ^2J(CF) = 22 Hz), 103.5 (dn), 89.0 (u), 87.1 (dn), 61.1 (u), 29.0 (u), 13.7 (dn), 8.8 (dn); IR (neat, cm^{-1}) 2967, 1736, 1607, 1511, 1346, 1225, 1054, 1012, 832; HRMS-ESI *m*/*z* [M + Na] calcd for $C_{20}H_{20}O_4F_2Na$ 385.1227, found 385.1241.

2*β*,5*β*-Di(4-nitrophenyl)-4*β*-ethoxycarbonyl-4α-benzyl-1,3-dioxolane (4r). A dry round-bottomed flask was charged with $Rh_2(piv)_4$ (1 mg, 0.003 mmol) and the flask was evacuated and filled with nitrogen. Anhydrous CH_2Cl_2 (5 mL) and 4-nitrobenzaldehyde (302 mg, 2.00 mmol) were added, and the flask was cooled by a bath of dry ice/acetone. Ethyl 2-diazohydrocinnamate (102 mg, 0.50 mmol) was dissolved in 3 mL of anhydrous CH_2Cl_2 and added to the reaction mixture via syringe pump at a rate of 1 mL/h. Following addition, the reaction mixture was allowed to warm to room temperature and mesitylene (60 mg, 0.50 mmol) was added. ^{1}H NMR analysis was then performed and the diastereomer ratio was determined to be 84:16. The solvent was then removed and the residue was chromatographed on silica gel with 5−8% ethyl acetate/hexanes as the eluent to give 139 mg (59%) of the title compound as a white solid, mp 55−59 °C. Also isolated was 26 mg (11%) of **4r** (minor diastereomer) as a white solid. A similar experiment gave **4r** in 54% yield.

Spectoscopic data for **4r**: ^{1}H NMR ($CDCl_3$, 400 MHz, *δ*): 8.37 (d, *J* = 9.0 Hz, 2H), 8.28 (d, *J* = 9.0 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 2H), 7.62 (d, *J* = 8.9 Hz, 2H), 7.32−7.46 (m, 5H), 5.98 (s, 1H), 5.27 (s, 1H), 3.65 (m, 1H), 3.47 (m, 1H), 3.45 (d, *J* = 14.7 Hz, 1H), 3.30 (d, *J* = 14.7 Hz, 1H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 169.5 (u), 148.9 (u), 148.2 (u), 142.6 (u), 141.9 (u), 134.5 (u), 130.9 (dn), 130.8 (dn), 128.6 (dn), 127.5 (dn), 127.4 (dn), 123.7 (dn), 123.6 (dn), 103.2 (dn), 88.2 (u), 84.8 (dn), 61.5 (u), 40.2 (u), 13.7 (dn); IR (neat, cm^{-1}) 2364, 2343, 1736, 1520, 1497, 1439, 1345, 1291, 1200, 1085, 1013, 851, 746, 697. Anal. Calcd for $C_{25}H_{22}N_2O_8$: C 62.76, H 4.63, N 5.86, O 26.75. Found: C 62.77, H 4.71, N 5.74, O 26.49.

Spectroscopic data for **4r** (minor diastereomer): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (d, J = 8.5 Hz, 2H), 8.37 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.22 (m, 3H), 7.09 (m, 2H), 6.18 (s, 1H), 5.54 (s, 1H), 4.26 (m, 2H), 2.60 (d, J = 13.7 Hz, 1H), 2.45 (d, J = 13.7 Hz, 1H), 1.24 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9 (u), 148.9 (u), 148.2 (u), 142.8 (u), 142.2 (u), 134.4 (u), 129.8 (dn), 128.6 (dn), 128.3 (dn), 128.0 (dn), 127.3 (dn), 123.9 (dn), 123.8 (dn), 102.6 (dn), 87.3 (u), 83.8 (dn), 62.2 (u), 41.7 (u), 14.2 (dn).

2*β*,5*β*-Di(2-naphthyl)-4*β*-*tert*-butoxycarbonyl-4α-benzyl-1,3-dioxolane (4s(*t*Bu)). A dry round-bottomed flask was charged with $Rh_2(piv)_4$ (1 mg, 0.003 mmol) and the flask was evacuated and filled with nitrogen. Anhydrous CH_2Cl_2 (5 mL) and 2-naphthaldehyde (283 mg, 1.81 mmol) were added, and the flask was cooled by a bath of dry ice/acetone. *tert*-Butyl 2-diazohydrocinnamate (105 mg, 0.45 mmol) was dissolved in 3 mL of anhydrous CH_2Cl_2 and was added to the reaction mixture via syringe pump at a rate of 1 mL/h. Following addition, the reaction mixture was allowed to warm to room temperature and mesitylene (54 mg, 0.45 mmol) was added. No diastereomers of **4s(*t*Bu)** were detected upon ^{1}H NMR analysis. The solvent was then removed and the residue was chromatographed on silica gel with 0.5−2.0% ethyl acetate/hexanes as the eluent to give 194 mg (83%) of the title compound as a white solid, mp 151−153 °C. A similar experiment gave the title compound in 73% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (m, 2H), 8.09 (d, J = 7.7 Hz, 2H), 7.99 (m, 2H), 7.91 (m, 3H), 7.70 (d, J = 8.8 Hz, 1H), 7.51−7.61 (m, 6H), 7.40 (app t, J = 7.7 Hz, 2H), 7.37 (m, 1H), 6.12 (s, 1H), 5.41 (s, 1H), 3.54−3.64 (m, 2H), 0.86 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8 (u), 136.0 (u), 134.4 (u), 133.9 (u), 133.4 (u), 133.1 (u), 132.9 (u, 2 carbons), 130.9 (dn), 128.6 (dn), 128.4 (dn, 2 carbons), 128.3 (dn, 2 carbons), 128.1 (dn), 127.9 (dn, 2 carbons), 127.7 (dn, 2 carbons), 126.9 (dn), 126.6 (dn), 126.3 (dn), 125.9 (dn), 125.0 (dn), 124.7 (dn), 104.3 (dn), 87.7 (u), 86.3 (dn), 81.7 (u), 41.6 (u), 27.2 (dn); IR (neat, cm^{-1}) 1737, 1602, 1451, 1342, 1220, 1161, 1125, 1086, 953, 904, 823, 731, 698; HRMS-ESI m/z [M+] calcd for $C_{35}H_{32}O_4Na$ 539.2198, found 539.2191.

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Supporting Information Available: Full experimental and characterization details for all compounds. copies of ^{1}H NMR and^{13}C NMR spectra for new compounds, and CIF files for compounds **4b**, **4k**, **4j**, **4r**, **4r** (minor), **4o**, **4s** and **4s** (minor), as well as a detailed explanation for stereochemical assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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