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Unusually Reactive and Selective Carbonyl Ylides for Three-Component Cycloaddition Reactions

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Abstract

Conditions are described for the Rh-catalyzed formation of highly-functionalized dihydro- and tetrahydrofuran products via three-component reactions of aldehydes, α -alkyl- α -diazoesters, and dipolarophiles. The alkyl-substituted carbonyl ylides that are generated in this fashion are highly reactive in cycloaddition reactions, and display a scope of reactivity that is much broader than three-component reactions of carbonyl ylides derived from ethyl diazoacetate or α -aryl- α -diazoesters. The reactions of alkyl-substituted carbonyl ylides proceed with high regioselectivity and diastereoselectivity that are rationalized by an asynchronous, *endo*-selective transition state.

INTRODUCTION

Dipolar cycloadditions are powerful reactions that rapidly build structurally complex heterocycles, and the multicomponent nature of dipolar cycloaddition reactions have been used to great effect in discovery chemistry.¹ Metal-catalyzed cycloadditions involving carbonyl ylides can generate stereochemically complex products from three simple starting materials.² The scope of such cycloadditions is broad when carbonyl ylides are formed by intramolecular processes.² In contrast, analogous three-component reactions involving aldehydes, diazo compounds and dipolarophiles had been relatively limited in terms of selectivity and substrate scope.³ Because of competing dioxolane formation,^{3a,4,5} the scope is generally limited to highly activated dipolarophiles (e.g. maleate), and mixtures of regio- and stereoisomers are often obtained.

In an elegant study, Jamison investigated the Rh-catalyzed reactions of carbonyl ylides derived from trimethylsilyldiazomethane and dicobalt-hexacarbonyl complexes of propargyl aldehydes.^{3e} The diastereoselectivity and the substrate scope of the Jamison system was high. However, regioselectivity was an issue for many of those transformations.^{3e} Muthusamy described Rh-catalyzed reactions of cyclic diazoamides, aldehydes and dimethyl acetylenedicarboxylate that proceed with high diastereoselectivity, but regioselectivity was low when ethyl acrylate was substituted as the dipolarophile.^{3f} Nair demonstrated that reactions of diazomalonate, aromatic aldehydes, and β -nitrostyrene proceed with high regio- and stereocontrol.^{3g} Despite these considerable advances, there was still not a general three-component method for combining aldehydes, diazo compounds and dipolarophiles with broad scope and control over regio- and diastereoselectivity. Accordingly, we sought to develop three-component reactions that would parallel the large scope of cycloadditions with cyclic carbonyl ylides.²

We recently demonstrated that carbonyl ylides of structure **1** could be generated from α -alkyl- α -diazoesters at low temperature with catalytic Rh_2Piv_4 .^{4g} Such ylides were not previously accessible due to the propensity of the precursor Rh-carbenoids to undergo β -hydride elimination.⁶ Ylides **1** were shown to react with excess aldehyde at -78°C to produce dioxolanes in high diastereoselectivity. We reasoned that the alkyl substituents of **1** destabilize the formal negative charge on the ylide, and consequently that ylides **1** should display enhanced reactivity toward exogenous dipolarophiles (Scheme 1). Herein, it is demonstrated that Rh_2Piv_4 catalyzed, three-component reactions of aldehydes, α -alkyl diazoesters and dipolarophiles give a diverse range of tetrahydrofuran (**2**) or dihydrofuran products (Scheme 1) with an unusual reaction scope and high selectivity. The high regio- and diastereoselectivity is rationalized by the asynchronous, *endo*-transition state displayed in Scheme 1.

RESULTS AND DISCUSSION

Dirhodium tetrapivalate has previously been shown^{4g} to be an efficient catalyst for the formation of carbonyl ylides from α -alkyl- α -diazoesters and benzaldehyde derivatives. It was found that methyl vinyl ketone was able to intercept the carbonyl ylide generated from benzaldehyde and *tert*-butyl 2-diazo-*trans*-hydrocinnamate in the presence of Rh_2Piv_4 at -78°C to form the functionalized tetrahydrofuran product with high regio- and diastereoselectivity. Following an optimization study (Table 1), it was found that yields were the highest when benzaldehyde was used as the limiting reagent with a small excess of *tert*-butyl 2-diazo-*trans*-hydrocinnamate and methyl vinyl ketone. However, when these conditions were applied to the analogous system with *tert*-butyl 2-diazo-*trans*-propanoate, the reaction did not go to completion and yields were lower. For this system, as well as for other in which the diazoester is substituted with a simple alkyl chain ($\text{R} = \text{Me}, \text{Bu}$), it was necessary for 1.7 equivalents of diazo compound to be used to push the reaction to near-completion. Hashimoto's dirhodium tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] catalyst⁷ was tested for asymmetric induction in the reaction of *p*-anisaldehyde, *tert*-butyl 2-diazo-*trans*-hydrocinnamate, and methyl vinyl ketone, however the product that was obtained was racemic. $\text{Rh}_2(\text{OAc})_4$ and $\text{Cu}(\text{acac})_4$ were also examined as catalysts in the reaction between methyl vinyl ketone, benzaldehyde and *tert*-butyl 2-diazo-*trans*-hydrocinnamate at -78°C . β -Hydride elimination predominated with $\text{Rh}_2(\text{OAc})_4$, and tetrahydrofuran **5** ($\text{R} = \text{Bn}$) was obtained in less than 20% yield. The tetrahydrofuran products were not formed at all in the reaction with $\text{Cu}(\text{acac})_2$, which lead to products that we have not yet been able to identify.

The conditions from Table 1 were applied to a variety of alkynes and alkenes with a single activating group to give products **3–7** (Scheme 2). Successful reactivity was observed for α -diazo-*trans*-propanoate, α -diazo-*trans*-butanoate, α -diazo-*trans*-octanoate, α -diazo-5-methylhexanoate, α -diazo-4-[1,3]dioxolan-2-yl-butanoate, and α -diazo-*trans*-hydrocinnamate with a range of aromatic aldehydes or with propargyl aldehydes. Dipolarophiles include methyl propiolate, ethyl acrylate, methyl vinyl ketone, acrylonitrile and propargyl methyl ketone. Prior use of such dipolarophiles in three-component reactions with carbonyl ylides had been limited, and in those instances $\leq 3:1$ regioselectivity was observed.^{3e,f} The 3-component reactions in Scheme 2 generally proceeded with excellent selectivity: high selectivity ($>88:12$) was observed for 11 of the 12 examples in Scheme 2, and only one isomer ($>95:5$) was observed in 7 cases. The exceptional case was the reaction of acrylonitrile, benzaldehyde and *tert*-butyl 2-diazo-*trans*-hydrocinnamate, which proceeded to give **7** with high regioselectivity but with poor stereoselectivity. For the formation of **5f**, cyclopentane formation via intramolecular C–H activation was a competing side reaction, but the use of excess benzaldehyde (4.0 equiv) and dipolarophile (4.0 equiv) did give **5f** in acceptable yield (51%). By contrast, intramolecular C–H activation was not a competing side reaction for the formation of **5e** from *tert*-butyl α -diazo-5-methylhexanoate.

More highly substituted dipolarophiles also combine efficiently with alkyl substituted carbonyl ylides to give products **8–17**, as shown in Scheme 3. Of the dipolarophiles in Scheme 3, only maleic anhydride and dimethyl acetylenedicarboxylate have been utilized previously^{2b,2d,3b} in 3-component reactions involving carbonyl ylides. Unsymmetrical dipolarophiles also react efficiently with alkyl-substituted carbonyl ylides: the reactions of cyclohexenone, methyl methacrylate, and dimethyl 2-ethylidenemalonate proceed with high regioselectivity to give **8**, **11** and **17**, respectively. Diethyl azodicarboxylate successfully leads to the tetrahydrooxa-3,4-diazole **10**. Strain can also be used to activate dipolarophiles:^{3e,8} prochiral cyclopropene **13** and chiral cyclopropene **15** react efficiently to give **14** and **16**, respectively. Excellent regio- and diastereoselectivity (>95:5) was observed in all cases in Scheme 3 except for the reaction of methyl methacrylate, which gave **11** with 1:1 diastereoselectivity, and the reaction of maleic anhydride which gave **9b** with 91:9 diastereoselectivity. A variety of functional groups are tolerated by the reactions in Schemes 2 and 3, including esters, alkynes, nitriles, oxazolidinones, alcohols, nitro-groups, and methoxy groups.⁹ As in the formation of **5f**, cyclopentane formation via intramolecular C–H activation was a competing side reaction for the formation of **12b**. However, the use of excess 4-fluorobenzaldehyde (4.0 equiv) and dipolarophile (4.0 equiv) gave **12b** in good yield (63%).

The reactions in scheme 2 and scheme 3 are subject to some limitations. Attempts to use 1-hexene, phenyl acetylene, norbornene, and vinyl trimethylsilane were unsuccessful, and led primarily to dioxolane products. An attempt to utilize *tert*-butyl α -diazoisovalerate led only to β -hydride elimination. Reactions with dimethyl maleate, ethyl-*trans*-crotonate, 3-pentyn-2-one, and acrolein gave the desired products in very low yield ($\leq 10\%$). When alkyl aldehydes were used (propionaldehyde and pivaldehyde), only β -hydride elimination was observed. An attempt to utilize *tert*-butyl α -diazo- α -cyclohexylacetate led only to β -hydride elimination.

The generation and rapid reactivity of alkyl-substituted carbonyl ylides at low temperature is key to selective reactivity. At higher temperatures, the selectivity and yields are poor. When *tert*-butyl 2-diazo-*trans*-hydrocinnamate is reacted with benzaldehyde and methyl vinyl ketone at rt, the tetrahydrofuran product is formed in only 16% yield, while the amount of β -hydride elimination (68% based on the diazo compound) is increased. Analogous reactions of ethyl diazoacetate or methyl phenyldiazoacetate with benzaldehyde and ethyl acrylate are less successful at -78°C or at rt: The reaction with ethyldiazoacetate forms primarily diethyl maleate and diethyl fumarate at -78°C or at rt. The reaction with methyl phenyldiazoacetate formed the desired product in low yield (31% based on ^1H NMR analysis) with competing epoxide¹⁰ formation (18%); the remainder of the mass balance was unreacted aldehyde (16%) and a complex mixture of products.

To demonstrate that the cycloaddition was complete at -78°C , the reaction of benzaldehyde, *tert*-butyl 2-diazo-*trans*-hexanoate, and methyl propiolate was carried out according to the general procedure. Following the addition of the diazo compound, the reaction was allowed to stir at -78°C for five minutes; then ethyl propiolate was added (1.1 equiv) and the reaction was allowed to warm up to room temperature. Analysis of the crude ^1H NMR spectrum revealed that cycloaddition had only occurred with methyl propiolate. A control experiment was run in which both methyl propiolate (1.1 equiv) and ethyl propiolate (1.1 equiv) were added prior to diazo addition. Crude ^1H NMR analysis revealed a $\sim 1:1$ mixture of both cycloadducts.

Regio- and stereochemical assignments were made on the basis of X-ray crystal structures for compounds **5b**, **9a**, and **14**; NOE experiments on **17** and on both diastereomers of compound **3c**; and chemical shift anisotropy analysis of the ^1H NMR spectra for all compounds. In the majority of the cases studied, the major product arises from an *endo* approach of the dipolarophile to the ylide conformer **A** (Figure 2). An exceptional case was compound **17** derived from dimethyl 2-ethylidenemalonate in which the major product was formed by *exo*

approach to the conformer **A**. *Exo/endo* isomers were also observed for **7** and **11**, in which the dipolarophiles were acrylonitrile and methyl methacrylate, respectively. Products arising from cycloaddition with the minor ylide conformer, conformer **B**, were observed for **3c** and **3d** where propargyl aldehydes were employed. The minor isomers of **4a**, **4b**, **5d** and **9b** were not definitively assigned, but in analogy to our prior observations in dioxolane formation,^{4g} we assume that they also arise from *endo* approach of the dipolarophile to the minor ylide conformer **B**.

When cyclopropenes **13** and **15** are used as dipolarophiles, the cyclopropene controls the *endo*-selectivity of the cycloadditions to provide the cycloaddition adducts **14** and **16** as single diastereomers. The sense of diastereoselectivity is in accord with that observed by Molchanov and coworkers in reactions between cyclic carbonyl ylides and substituted cyclopropenes.⁸ With the trisubstituted cyclopropene **15**, the regioselectivity of dipolar cycloaddition is apparently controlled by steric considerations: the preferred regioisomer is derived from the transition state where the less substituted end of the cyclopropene is aligned with the more substituted end of the carbonyl ylide, as shown in Figure 3.

CONCLUSIONS

In summary, general conditions are described for the Rh-catalyzed formation of highly-functionalized dihydro- and tetrahydrofuran via three-component reactions of aldehydes, α -alkyl- α -diazoesters, and dipolarophiles with selectivity over dioxolane formation. Alkyl substituted carbonyl ylides are highly reactive in such transformations, and the scope of reactivity is broad relative to analogous carbonyl ylides derived from ethyl diazoacetate or α -aryl- α -diazoesters. Products are formed in good yields and with excellent regio- and diastereoselectivity when the reactions are carried out at $-78\text{ }^{\circ}\text{C}$ in the presence of catalytic Rh_2Piv_4 . A model invoking an asynchronous, *endo* transition state is proposed to explain the nature of diastereoselectivity.

EXPERIMENTAL SECTION

Representative procedure for three component dipolar cycloaddition reactions: synthesis of 4-acetyl-2 α -ethyl-5 β -phenyl-tetrahydrofuran-2 β -carboxylic acid ethyl ester (**5a**)

In a flame-dried round bottomed flask, Rh_2Piv_4 (1.5 mg, 0.002 mmol), benzaldehyde (54 mg, 0.51 mmol), and methyl vinyl ketone (39 mg, 0.56 mmol) were dissolved in anhydrous CH_2Cl_2 (2.5 mL) and cooled by a bath of dry ice/acetone ($-78\text{ }^{\circ}\text{C}$) under a nitrogen atmosphere. *tert*-Butyl 2-diazobutanoate (146 mg, 0.86 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) and added to the reaction mixture over 1 hour via syringe pump. After the addition was complete, the reaction mixture was allowed to stir for an additional 5 minutes and was then allowed to warm up to room temperature. Mesitylene (61 mg, 0.51 mmol) was added to the reaction mixture and an ^1H NMR spectrum was taken to estimate the yield and isomer ratio (s). The solvent was subsequently removed and the residue was chromatographed on silica gel to give 123 mg (0.39 mmol, 76%) of **5a** as a colorless oil. A similar experiment starting with 50 mg (0.47 mmol) of benzaldehyde, 37 mg (0.52 mmol) of methyl vinyl ketone, and 136 mg (0.80 mmol) of *tert*-butyl 2-diazobutanoate gave 124 mg (0.39 mmol, 83%) of **5a**. ^1H NMR (400 MHz, CDCl_3 , δ): 7.43-7.38 (m, 2H), 7.33-7.21 (m, 3H), 5.32 (d, $J = 7.2\text{ Hz}$, 1H), 3.46 (app dt, $J = 7.6\text{ Hz}$, 3.5 Hz, 1H), 2.85 (dd, $J = 13.5\text{ Hz}$, 3.5 Hz, 1H), 2.07 (dd, $J = 13.3\text{ Hz}$, 7.4 Hz, 1H), 2.00-1.88 (m, 1H), 1.82-1.72 (m, 1H), 1.59 (s, 9H), 1.42 (s, 3H), 0.98 (t, $J = 7.4\text{ Hz}$, 3H); ^{13}C NMR (100 MHz, CDCl_3 , δ): 207.2 (u), 172.6 (u), 138.1 (u), 128.4 (dn), 128.0 (dn), 126.5 (dn), 87.0 (u), 82.9 (dn), 81.0 (u), 57.0 (dn), 37.8 (u), 32.4 (u), 30.5 (dn), 28.0 (dn), 8.58 (dn); IR (CHCl_3 , cm^{-1}): 2981, 2937, 1731, 1714, 1615, 1457, 1370, 1254, 1124, 1061, 908, 845, 701, 662; HRMS-ESI m/z : $[\text{M}+\text{Na}]$, calcd for $\text{C}_{19}\text{H}_{26}\text{O}_4\text{Na}$, 341.1729; found 341.1719.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Mixing experiment

Figure 2.
Proposed model to explain diastereoselectivity

Figure 3.
Proposed model for the formation of **17**

Scheme 1.
Cycloadditions of alkyl-substituted carbonyl ylides

Scheme 2. Three-component coupling reactions of dipolarophiles with a single activating group

^aTwo diastereomers were detected upon analysis of the 1H NMR spectrum of the crude. Other isomeric materials were not detected. ^bYield of both diastereomers. ^cYield of diastereomer shown. ^dThe reaction was carried out with 1.0 equiv of *t*-butyl- α -diazooctanoate, 4.0 equiv of benzaldehyde and 4.0 equiv. of methyl vinyl ketone. ^eThe relative stereochemistry of the minor isomer was not determined. ^fStereochemical assignments were made on the basis of 1H NMR analysis (see Supporting information).

Scheme 3. Three-component coupling reactions of dipolarophiles with multiple substituents
 Diastereomer ratios were determined by analysis of the 1H NMR spectra of the crude: no other isomeric materials were observed. ^aIsolated yield of diastereomer shown. ^bIsolated yield of both diastereomers. ^cThe reaction was carried out with 1.0 equiv of *t*-butyl- α -diazoctanoate, 4.0 equiv of 4-fluorobenzaldehyde and 4.0 equiv. of dimethyl acetylenedicarboxylate. ^dStereochemical assignments were made on the basis of 1H NMR analysis (see Supporting information).

Table 1
Optimization Study

entry	PhCHO (equiv)	Diazo compound (equiv)	methyl vinyl ketone (equiv)	yield of 5 ^a
1	1.1	1.0	4.0	53%
2	1.0	1.5	4.0	78%
3	1.0	2.0	4.0	78%
4	1.0	1.5	2.0	85%
5	1.0	1.5	1.1	81%
6	1.0	1.3	1.1	84%
7	1.0	1.1	1.1	76%
8	1.0	1.5	1.1	16%
9	1.0	1.3	1.1	56%
10	1.0	1.5	1.1	69%
11	1.0	1.7	1.1	77%
12	1.0	1.9	1.1	76%

{ R=Bn (entries 4-8)
 { R=Et (entries 9-12)

^aNMR yield

^bReaction was carried out at room temperature