ORGANIC LETTERS

2005
Vol. 7, No. 1
83−86

Three-Component Reaction of Aryl Diazoacetates, Alcohols, and Aldehydes (or Imines): Evidence of Alcoholic Oxonium Ylide Intermediates

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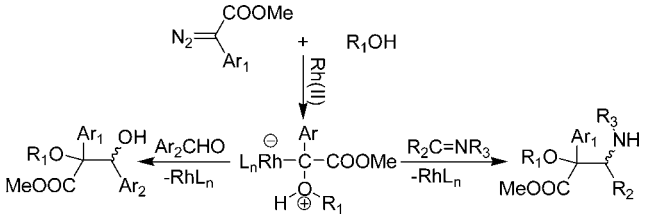
Received October 19, 2004

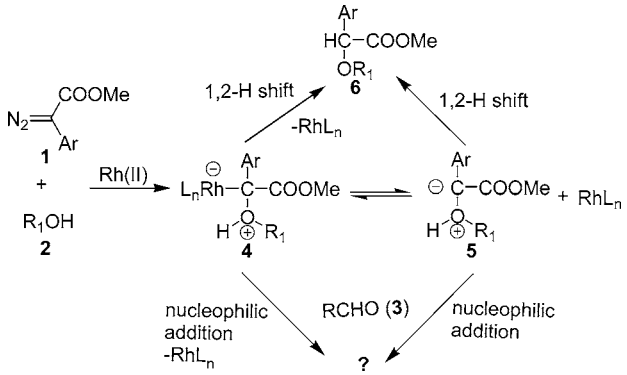
ABSTRACT



The Rh(II)-catalyzed three-component reaction of aryl diazoacetates, alcohols and aldehydes was explored, which provided evidence of alcoholic oxonium ylide formation for O–H insertion. A new C–C bond formation reaction where alcoholic oxonium ylides were trapped by electron-deficient aryl aldehydes (or imines) was realized.

Oxygen−hydrogen insertion by catalytic reactions of diazo compounds has drawn a great deal of interest because of its ability to provide a direct entry to C−O bond formation.[1] However, the mechanism of this reaction is not fully understood. The suggestion has been made that the insertion occurs stepwise via initial oxonium ylide formation followed by a rapid 1,2-hydrogen shift (Scheme 1, **4**/**5** to **6**).[2] Yet experimental evidence to support this mechanism is lacking. There is a recent report on the electronic effects of Rh(II) carbene O−H insertion, where the Hammett correlation data support a concerted reaction pathway that is similar to the well-established C−H insertion.[3] We report here evidence for the stepwise ylide-mediated reaction pathway rather than the concerted insertion.

Scheme 1. Possible C−C Bond Formation Reaction of Alcoholic Oxonium Ylides



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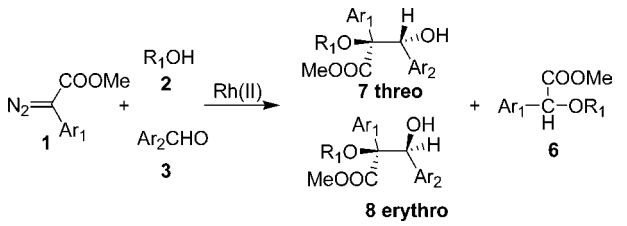
10.1021/ol0478483 CCC: $30.25
Published on Web 12/09/2004

Our experimental system is the rhodium(II)-catalyzed three-component reaction of methyl phenyl diazoacetate with alcohols in the presence of aldehydes/imines. We have previously shown that ammonium ylides generated from diazo compounds and arylamines underwent aldol-type nucleophilic addition reactions.[4] We hypothesized that an alcoholic oxonium ylide,[5] similar to an ammonium ylide, generated in situ from a diazo compound and an alcohol may be trapped similarly by an electrophile such as an aldehyde or imine (Scheme 1). The stepwise mechanism can be demonstrated by showing a correlation of the degree of oxonium ylide trapping with the generation of product **6** by 1,2-hydrogen shift (O−H insertion). The chemoselectivity of this reaction can be systematically studied by changing the alcohols, aldehydes, and diazo compounds.

Methyl phenyl diazoacetate (**1a**, Ar_1 = Ph) and benzyl alcohol (**2a**, R_1 = Bn) were found to react with *p*-nitrobenzaldehyde (**3a**, Ar_2 = *p*-NO_2Ph) to generate the desired three-component products **7a** + **8a** in 70% yield with 43:57 dr (**7a**:**8a**) favoring the *erythro*-isomer (Scheme 2, Table 1, entry 1). The stereochemistry of isomers **7** was confirmed by the analogue **7j**, which was assigned with the single-crystal X-ray structure (Figure 1). The O−H insertion product **6a** (Ar_1 = Ph, R_1 = Bn) was formed in a 13:87 ratio (**6a**:**7a**+**8a**). There was no formation of epoxide from reaction of **1a** with *p*-nitrobenzaldehyde (**3a**) in this case. In contrast, **6a** was the only product in the absence of aldehyde **3a**, and epoxidation with **3a** was the only reaction in the absence of alcohol **2a**.[6] Furthermore, control experiments indicated that the formation of **7a**/**8a** is neither from a ring opening reaction of the epoxide (from **3a**) with alcohol **2a** nor from the O−H insertion product **6a** with aldehyde **3a** (Scheme 3).

Scheme 2



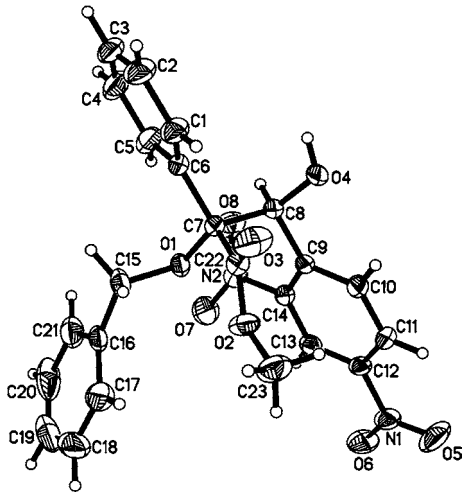


Figure 1. ORTEP representation of the crystal structure of **7j**.

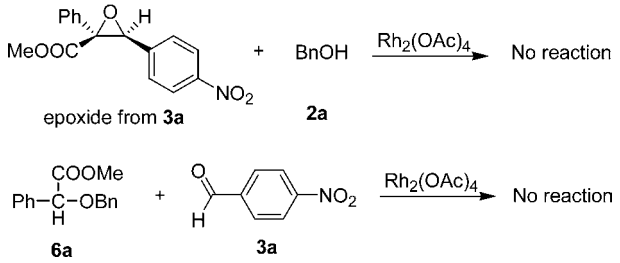
The reaction chemoselectivity was found to be dependent on electronic and steric features of the alcohol used. Electron-rich and less hindered alcohols favored the alcoholic oxonium ylide formation, and the oxonium ylide derived from electron-rich alcohols favored the three-component product. Examples are (1) *p*-methoxybenzyl alcohol gave higher yield and better selectivity than benzyl alcohol, favoring the three-

Table 1. Three-Component Reaction of Aryl Diazoacetate, Alcohols, and Aldehydes (Scheme 2)[a]

entry	Ar_1	R_1	Ar_2	products	yield[b] (%)	dr (**7**:**8**)[c]	**7**+**8**:**6**[c]
1[d]	Ph	Bn	*p*-NO_2Ph	**7a** + **8a**	70	43:57	87:13
2[d]	Ph	PMB	*p*-NO_2Ph	**7b** + **8b**	83	42:58	95:5
3[d,e]	Ph	H	*p*-NO_2Ph	**7c** + **8c**	65	50:50	92:8
4[d]	Ph	Me	*p*-NO_2Ph	**7d** + **8d**	48	41:59	71:29[f]
5[d]	Ph	^{t}Bu	2,4-$(NO_2)_2$Ph	**7e** + **8e**	18	88:12	*g*
6[h]	Ph	PMB	*p*-NO_2Ph	**7b** + **8b**	76	38:62	97:3
7[h]	Ph	PMB	*o*-NO_2Ph	**7f** + **8f**	47	67:33	64:36
8[h]	Ph	PMB	*p*-CF_3Ph	**7g** + **8g**	56	35:65	62:38
9[h]	Ph	PMB	*p*-CNPh	**7h** + **8h**	51	29:71	57:43
10[d,i]	Ph	Bn	*p*-MeOPh	**7i** + **8i**	56	33:67	77:23
11[d]	Ph	Bn	2,4-$(NO_2)_2$Ph	**7j** + **8j**	78	82:18	89:11
12[d]	PMP	Bn	*p*-NO_2Ph	**7k** + **8k**	87	38:62	92:8
13[d]	*trans*-styryl	Bn	*p*-NO_2Ph	**7l** + **8l**	50	56:44	69:31
14[h,j]	Ph	PMB	*p*-CF_3Ph	**7g** + **8g**	64	32:68	71:29
15[h,k]	Ph	PMB	*p*-CF_3Ph	**7g** + **8g**	40	26:74	46:54

[a] All reactions were carried out in refluxing CH_2Cl_2 in the presence of $Rh_2(OAc)_4$ (1 mol %) with Ar_1=Ph unless otherwise indicated. [b] Isolated yields after chromatography. [c] Determined by ^{1}H NMR of crude reaction mixtures. [d] **1**:**2**:**3** = 1.0:1.1:1.1 mmol. [e] Performed at 40 °C in THF. [f] **7**+**8**:**6**:epoxide = 64:26:10. [g] No formation of **6**. [h] **1**:**2**:**3** = 1.3:1.0:1.5 mmol. [i] 1.1 mmol of Ti(O^tBu)$_4$ was used. [j] Rh_2(tfa)$_4$ as catalyst. [k] Rh_2(*S*-DOSP)$_4$ as catalyst.

Scheme 3

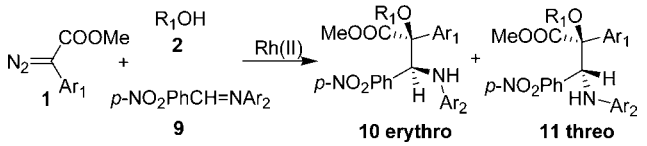


component formation (Table 1, entry 2 vs entry 1); (2) whereas methanol gave moderate yield of the three-component products along with O−H insertion and epoxidation (Table 1, entry 4), the epoxide of *p*-nitrobenzaldehyde[6] was the major product with bulky ^{t}BuOH accompanying a lower yield of three-component products **7**/**8** (Table 1, entry 5). Electron-deficient phenols such as phenol, *p*-methoxyphenol, and *p*-nitrophenol led to only epoxide formation.

Reaction of methyl *p*-methoxyphenyl diazoacetate, a more electron-rich diazo compound than methyl phenyl diazoacetate, with benzyl alcohol and *p*-nitrobenzaldehyde gave a three-component product in 87% isolated yield along with a small amount of O−H insertion (Table 1, entry 12). This is in agreement with the rationale that electron-rich alcoholic oxonium ylides favor the three-component reaction. Different aldehydes were tested for the trapping. Electron-deficient aryl aldehydes gave the desired three-component products in moderate to good yields (Table 1, entries 6−9). Electron-rich aromatic aldehydes such as *p*-anisaldehyde gave no three-component product due to reduced eletrophilicity. We anticipated that adding additional Lewis acid would promote the reaction by activating the aldehyde. In fact, Ti(O^tBu)$_4$ was found to be the choice among Lewis acids including Ti(O^iPr)$_4$, $TiCl_4$, and BF_3·Et_2O. The three-component product was obtained in 56% isolated yield with *p*-anisaldehyde in the presence of 1.1 equiv of Ti(O^tBu)$_4$ (Table 1, entry 10),[7] suggesting a stepwise reaction pathway for the three-component reaction, (1) alcoholic oxonium ylide formation and (2) nucleophilic attack of the ylide to an aldehyde. It is worthwhile to note that water serves as an "active alcohol" to afford a three-component product α,*β*-dihydroxyl esters (**7c** + **8c**) in moderate yield (Table 1, entry 3).

The oxonium ylide was also successfully trapped with imines. When aryl imines **9** were employed, the reactions yielded highly substituted α-alkoxy-*β*-alkylamino esters (Scheme 4) in moderate to good yields, and with improved

Scheme 4



diastereoselectivities favoring *erythro*-isomers. Hydrolysis of the isomers of esters **10c** + **11c** gave the corresponding amino acids, and the major isomer **12c** of amino acids was crystallized as a pure diastereomer. We determined the stereochemistry of **10c** through the X-ray crystal structure of **12c** (Figure 2). This process was demonstrated to build

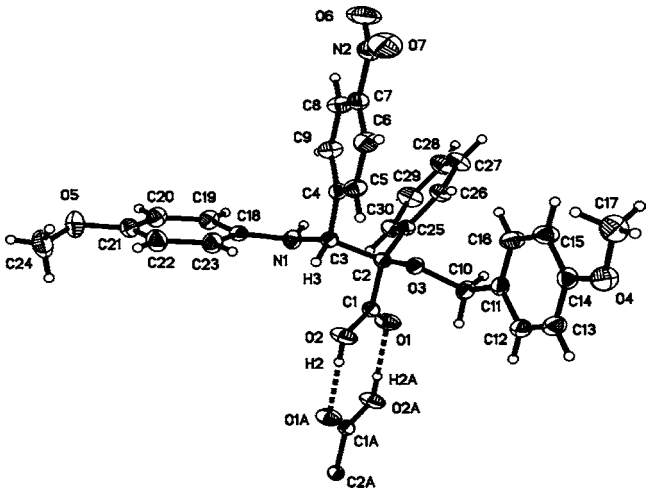


Figure 2. ORTEP representation of the crystal structure of **12c**.

highly substituted α-alkoxy-*β*-amino acid **12c** in large scale. Greater than 16 g of **12c** was prepared from this atom-efficient three-component reaction.

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To address if the oxonium ylide intermediate was metal-associated **4** or metal-free **5** (Scheme 1), several Rh(II) catalysts bearing different ligands including $Rh_2(tfa)_4$, Rh_2(*S*-DOSP)$_4$, $Rh_2(cap)_4$, and Rh_2(*S*-nttl)$_4$ were employed (Table 1, entries 8, 14, 15 and Table 2, entries 1, 5−8).[8]

Table 2. Three-Component Reaction of Aryl Diazoacetate, Alcohols, and Imines (Scheme 4)[a]

entry	Ar_1	R_1	Ar_2	products	yield[b] (%)	dr (**10**:**11**)[c]
1	Ph	Bn	Ph	**10a** + **11a**	70	85:15
2	Ph	PMB	Ph	**10b** + **11b**	74	82:18
3	Ph	PMB	PMP	**10c** + **11c**	62	79:21
4	PMP	Bn	Ph	**10d** + **11d**	57	81:19
5[d]	Ph	Bn	Ph	**10a** + **11a**	79	80:20
6[e]	Ph	Bn	Ph	**10a** + **11a**	65	82:18
7[f]	Ph	Bn	Ph	**10a** + **11a**	81	68:32
8[g]	Ph	Bn	Ph	**10a** + **11a**	29	77:23

[a] All reactions were carried out in refluxing CH_2Cl_2 in the presence of $Rh_2(OAc)_4$ (1 mol %) with **1**:**2**:**9** = 1.0:1.1:1.1 mmol.. [b] Isolated yield after purification. [c] Ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. [d] Rh_2(*S*-DOSP)$_4$ as catalyst. [e] Rh_2(*S*-nttl)$_4$ as catalyst. [f] $Rh_2(tfa)_4$ as catalyst. [g] $Rh_2(cap)_4$ as catalyst.

Significant changes in both chemoselectivity and diastereoselectivity were observed with the catalysts. For example, $Rh_2(tfa)_4$ gave a higher yield of the three-component products and suppressed the O−H insertion product better than Rh_2(*S*-DOSP)$_4$ (Table 1, entry 14 vs entry 15). Because electron-withdrawing ligands on Rh(II) retard the O−H insertions,[2,9] there may be more opportunity for nucleophile attack on aldehydes. Changes in diastereoselectivity were also observed in some cases (Table 1, entry 8 vs entry 15, dr from 35:65 to 26:74 and Table 2, entry 1 vs entry 7, dr from 85:15 to 68:32). The catalyst dependence of chemoselectivity and diastereoselectivity support the rationale that alcoholic oxonium ylide intermediates are metal-associated. Unfortunately, racemic products were obtained by using Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-nttl)$_4$.

In conclusion, we report here the first example of Rh(II)-catalyzed three-component reactions of aryl diazoacetates, alcohols, and aldehydes/imines. Our data suggests that the reaction occurs through a metal-associated alcoholic oxonium ylide intermediate and is followed by a nucleophilic addition to an electrophile, providing evidence of alcoholic oxonium ylide formation for O−H insertion. This work provides a convenient route to α,*β*-dihydroxy acid and α-hydroxy-*β*-amino acid derivatives that are important compounds in organic and medicinal chemistry.

Acknowledgment. We thank Prof. Michael P. Doyle from the University of Maryland for helpful discussions. We thank Prof. Kai-Bei Yu from Chengdu Institute of Organic Chemistry and Prof. Zhong-Yuan Zhou from The Hong Kong Polytechnic University for X-ray measurements. We are grateful for financial support from the National Science Foundation of China (Grant no. 20472080).

Supporting Information Available: Experimental procedures and characterization data of all new compounds and X-ray crystallographic data of **7j** and **12c** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) It is notable that no reaction occurs in the absence of catalyst $Rh_2(OAc)_4$.

(8) $Rh_2(tfa)_4$ = rhodium trifluroacetate; Rh_2(*S*-DOSP)$_4$ = dirhodium tetrakis(*S*-(*N*-dodecylbenzenesulfonyl) prolinate); $Rh_2(cap)_4$ = rhodium caprolactam; Rh_2(*S*-nttl)$_4$ = dirhodium tetrakis(*S*-(*N*-1,8-naphthoyl) *tert*-leucinate).

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