The rhodium catalyzed three-component reaction of diazoacetates, titanium(IV) alkoxides and aldehydes†

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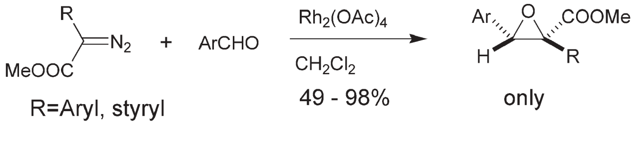
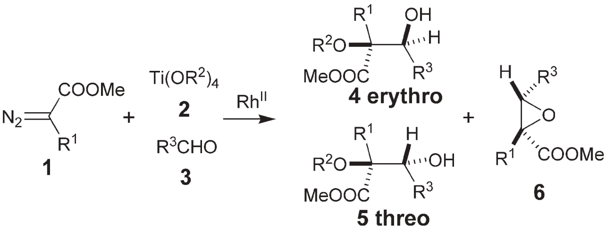
The rhodium(II)-catalyzed three-component reaction of diazoacetates, titanium alkoxides and aldehydes is shown to give α-alkoxyl-β-hydroxyl acid derivatives; the novel C–C bond formation reaction is proposed to occur through oxonium ylides derived from diazo compounds and titanium alkoxides, and followed by intermolecular trapping by aldehydes.

The transition metal-catalyzed decomposition of diazocarbonyl compounds is an attractive transformation in organic synthesis.[1] The rhodium-catalyzed reaction in the presence of aldehydes normally leads to 1,3-dioxolanes[2] or epoxides[3] from carbonyl ylide intermediates.[4] On the other hand, Lewis acids such as $TiCl_4$, $SnCl_4$, *etc.* have been reported to catalyze reactions of diazo compounds with aldehydes; however, the process afforded nitrogen-free 3-hydroxyacrylates and β-dicarbonyl products instead of 1,3-dioxolanes.[1,5]

Doyle *et al.*[3a] and Davies *et al.*[3b] individually reported stereospecific epoxidation from the dirhodium(II)-catalyzed reaction of aryl- and styryldiazoacetates with aryl/styryl aldehydes. The reaction occurred through the intramolecular ring closure of a carbonyl ylide derived from the diazoacetates and the aldehydes (Scheme 1). It is worth mentioning that the reaction was limited to aromatic/styryl aldehydes; the use of aliphatic aldehydes gave a complex mixture. To our surprise, when the reaction was performed in the presence of both a dirhodium(II) catalyst and a titanium(IV) alkoxide, three-component coupling occurred to produce α-alkoxyl-β-hydroxyl esters **4** and **5** in moderate to good yield (Scheme 2). In this three-component reaction, an alkoxyl group was transferred from the titanium reagent to the product **4**/**5**. Excellent chemoselectivity and high diastereoselectivity was obtained with unbranched aliphatic aldehydes. To the best of our knowledge, this is the first example of a three-component reaction of diazoacetate, titanium(IV) alkoxide and aldehyde.[6]



Scheme 1 The catalyzed epoxidation of diazo compounds and aldehydes.



Scheme 2 The rhodium-catalyzed three-component reaction of diazoacetates, titanium(IV) alkoxides and aldehydes.

The first indication of this reaction occurred in the $Rh_2(OAc)_4$-catalyzed reaction of methyl phenyldiazoacetate (**1a**) with 1.1 equiv. of titanium(IV) isopropoxide (**2a**) and *p*-anisaldehyde (**3a**). Products **4a** and **5a** were obtained in 69% isolated yield with 68 : 32 diastereomeric ratio (dr) favoring the *erythro*-stereoisomer (Table 1, entry 1, R^1 = Ph, R^2 = *i*Pr, R^3 = *p*-methoxyphenyl). Epoxide **6a** was the main by-product (**6a** : (**4a** + **5a**) = 13 : 87) determined by ^1H NMR analysis of the crude reaction mixture. This novel three-component reaction reported here is essentially different from the rhodium-catalyzed three-component coupling reaction of diazoacetate, alcohol and aldehyde (or imine) reported in ref. 6c, in which the O–H insertion product derived from diazoacetate and alcohol in the presence of aldehyde was the main by-product.

Tests carried out with decreasing amounts of titanium reagent (Table 1, entries 1–3) led to a decrease of the product yield, down to 45% for 0.25 equiv. of titanium regent. A yield greater than 25% is indeed indicative that more than one isopropoxy group of $Ti(OiPr)_4$ is transferred in the reaction.

A control reaction of epoxide **6a** with titanium(IV) isopropoxide (**2a**) did not result in three-component products, indicating that **4a** and **5a** were not formed from the Lewis acid catalyzed ring opening of the corresponding epoxides (Scheme 3). It was interesting to find that no decomposition of diazo **1a** occurred with dirhodium acetate catalyst in the presence of 1.1 equiv. of titanium(IV) isopropoxide (**2a**) without benzaldehyde in the

Table 1 The three-component reaction of methyl phenyldiazoacetate (**1a**) with titanium(IV) isopropoxide (**2a**) and *p*-anisaldehyde (**3a**) with different ratios of reactants (Scheme 2)[a]

Entry	**1a** : **2a** : **3a**/mmol	%Yield (**4a** + **5a**)[b]	dr (**4a** : **5a**)[c]	(**4a** + **5a**) : **6a**[c]
1	1.0 : 1.1 : 1.1	69	68 : 32	87 : 13
2	1.0 : 0.5 : 1.1	58	66 : 34	66 : 34
3	1.0 : 0.25 : 1.1	45	57 : 43	57 : 43
4	1.0 : 0.0 : 1.1	0	N/A	0 : 100

[a] All reactions were carried out in refluxing CH_2Cl_2 in the presence of $Rh_2(OAc)_4$ (1 mol %). [b] Isolated yields after chromatography. [c] Determined by ^1H NMR of crude reaction mixtures.

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† Electronic supplementary information (ESI) available: experimental details, NMR assignments, analytical data and X-ray structures. See http://www.rsc.org/suppdata/cc/b5/b502093j/

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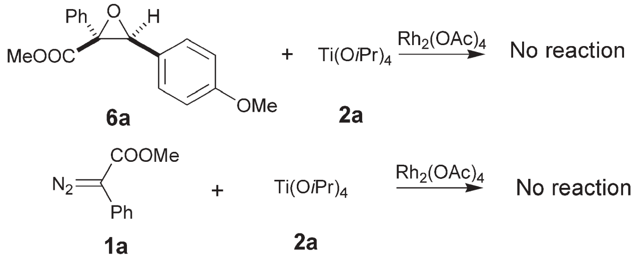


Scheme 3 Control experiments clarifying the proposed reaction pathway.

reaction. Total recovery of diazo compound **1a** was observed in this case (Scheme 3). In contrast, decomposition of diazoacetate **1a** with dirhodium acetate gave a mixture of 2,3-diphenyl fumarate and maleate in the absence of **2a**.[7,8] The three-component reaction occurred after an aldehyde was added to the unreacted mixture of **1a**, **2a**, and dirhodium acetate. This may be rationalized by the aldehyde retrieving reactivity of **1a** towards the dirhodium catalyst by competitive coordination with titanium complex **2a**.

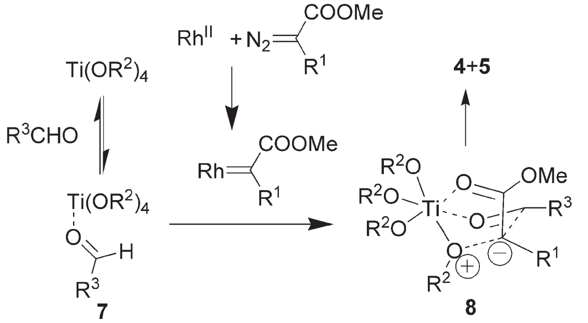
The three-component reaction was found to be quite general. In Table 2, the scope of the reaction with combinations of various aldehydes and titanium alkoxides was explored. Satisfactory yields were observed from aromatic aldehydes bearing either electron-withdrawing or electron-donating groups (entries 1–5). Unbranched or branched aliphatic aldehydes also gave a good yield of **4**/**5** (entries 8–10). An α,β-unsaturated aldehyde was also a good substrate (entry 7). However, the reaction was dramatically influenced by the steric effect of the titanium reagents. Better chemoselectivity was obtained by using less sterically hindered titanium(IV) alkoxides. A product ratio as high as 96 : 4 for (**4** + **5**) : **6** was obtained by using Ti(OEt)$_4$ or Ti(O*n*Pr)$_4$ (entries 11 and 12), and the ratio decreased to 89 : 11 with Ti(O*i*Pr)$_4$ (entry 2). The use of Ti(O*t*Bu)$_4$ gave only epoxide **6** with no three-component adducts **4**/**5** being observed.

The reaction was further expanded to other diazo compounds. The best result was obtained from the methyl *p*-methoxyphenyl diazoacetate, affording **4l**/**5l** in 92% yield and a moderate dr (Table 2, entry 13). Methyl *trans*-styryl diazoacetate was also successfully used to give a moderate yield of **4m**/**5m** in this reaction (Table 2, entry 14). Attempts to achieve three-component coupling with other electrophiles such as imines, ketones and α, β-unsaturated ketones were unsuccessful.

Also no obvious principle was found to explain the variable diastereomeric ratio of **4** : **5**. The reaction favors formation of the *erythro* diastereomer **4** with a dr as high as 95 : 5 with butyraldehyde, decreasing to 86 : 14 and 73 : 27 with the more hindered isobutyraldehyde and pivaldehyde, respectively. The stereochemistry of stereoisomer **4d** was confirmed by its X-ray structure.[8]

Although the mechanism for the formation of the three-component products **4** and **5** is unknown, a possible reaction pathway is proposed. The reaction is likely to proceed through an aldol-type nucleophilic addition of an oxonium ylide to the aldehyde, in which the ylide is generated from the carbenoid with an alkoxyl group of titanium(IV) alkoxide. The titanium reagent also serves as a Lewis acid to activate the aldehyde in proposed intermediate **8** (Scheme 4). The reason for the different ratios of **4** : **5** is unclear at this time and deserves further investigation.

In conclusion, we have developed the first example of a three-component reaction of diazoacetate, titanium(IV) alkoxide and aldehyde in the presence of dirhodium acetate catalyst. Titanium(IV) alkoxide plays a dual role as both reagent and activator. The novel C–O/C–C bond formation reaction gave



Scheme 4 Proposed mechanism of formation of α-alkoxyl-β-hydroxyl acid derivatives.

Table 2 The three-component reaction of diazoacetate with different titanium alkoxides and aldehydes (Scheme 2)[a]

Entry	R^1	R^2	R^3	Products	%Yield (**4** + **5**)[b]	dr (**4** : **5**)[c]	(**4** + **5**) : **6**[c]
1	Ph	*i*Pr	*p*-MeOPh	**4a** + **5a**	69	68 : 32	87 : 13
2	Ph	*i*Pr	Ph	**4b** + **5b**	71	75 : 25	89 : 11
3	Ph	*i*Pr	*p*-NO$_2$Ph	**4c** + **5c**	71	80 : 20	93 : 7
4	Ph	*i*Pr	*o*-NO$_2$Ph	**4d** + **5d**	70	83 : 17	n.d.[d]
5[e]	Ph	*i*Pr	*o*-NO$_2$Ph	**4d** + **5d**	90	85 : 15	n.d.[d]
6	Ph	*i*Pr	2,4-(NO$_2$)$_2$Ph	**4e** + **5e**	78	75 : 25	99 : 1
7	Ph	*i*Pr	(*E*)-styryl	**4f** + **5f**	55	53 : 47	62 : 38
8	Ph	*i*Pr	^{n}Pr	**4g** + **5g**	77	95 : 5	n.d.[d]
9	Ph	^{i}Pr	^{i}Pr	**4h** + **5h**	72	86 : 14	n.d.[d]
10	Ph	*i*Pr	^{t}Bu	**4i** + **5i**	60	73 : 27	n.d.[d]
11	Ph	Et	Ph	**4j** + **5j**	75	60 : 40	96 : 4
12	Ph	*n*Pr	Ph	**4k** + **5k**	75	66 : 34	96 : 4
13	PMP	*i*Pr	Ph	**4l** + **5l**	92	81 : 19	n.d.[d]
14	(*E*)-styryl	*i*Pr	Ph	**4m** + **5m**	49	61 : 39	78 : 22

[a] All reactions were carried out in refluxing CH$_2$Cl$_2$ in the presence of Rh$_2$(OAc)$_4$ (1 mol %) with **1** : **2** : **3** = 1.0 : 1.1 : 1.1 mmol unless otherwise indicated. [b] Isolated yields after chromatography. [c] Determined by ^{1}H NMR of crude reaction mixtures. [d] The data were not detected. [e] **1** : **2** : **3** = 1.3 : 1.0 : 1.0 mmol.

α-alkoxyl-β-hydroxyl acid derivatives in moderate to good yield with various aldehydes. Asymmetric induction of this reaction with a chiral titanium reagent is currently underway in our laboratories.

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7 The dimers were obtained as the only products when the reaction was performed under Ar. If the reaction was conducted under oxygen, no trace amount of dimers was detected, the oxidation product methyl benzoylformate accompanied by other by-products was obtained instead. For the experimental details and the X-ray structure of dimethyl 2,3-diphenyl maleate, see ESI.

8 Crystal data (λ = 0.71073 Å, the structure was solved by direct methods (SHELXL-97) and refined by full-matrix least-squares on F^2.): dimethyl 2,3-diphenyl maleate: $C_{18}H_{16}O_4$, M = 296.31, monoclinic, space group $P2_1/n$, a = 8.8668(12) Å, b = 8.7122(12) Å, c = 19.668(3) Å, α = 90°, β = 94.189(3)°, γ = 90°, V = 1515.3(4) Å^3, Z = 4, μ = 0.092 mm^{-1}, T = 294(2) K, 13787 reflections collected, 3507 unique (R_{int} = 0.0395). Final GooF = 1.059, R_1 = 0.0476, wR_2 = 0.1246, R indices based on 3507 reflections with $I > 2\sigma(I)$, 201 parameters, 0 restraints, CCDC 261327. Compound **4d**: $C_{19}H_{21}NO_6$, M = 359.37, monoclinic, space group $P2_1/c$, a = 13.289(2) Å, b = 8.1727(12) Å, c = 16.5883(3) Å, α = 90°, β = 91.999(3)°, γ = 90°, V = 1800.4(5) Å^3, Z = 4, μ = 0.099 mm^{-1}, T = 294(2) K, 16387 reflections collected, 4172 unique (R_{int} = 0.0357). Final GooF = 1.016, R_1 = 0.0399, wR_2 = 0.1091, R indices based on 4172 reflections with $I > 2\sigma(I)$, 241 parameters, 0 restraints, CCDC 261328. See http://www.rsc.org/suppdata/cc/b5/b502093j/ for crystallographic data in CIF or other electronic format.