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Novel C–C bond formation through addition of ammonium ylides to arylaldehydes: a facile approach to β-aryl-β-hydroxy α-amino acid frameworks†

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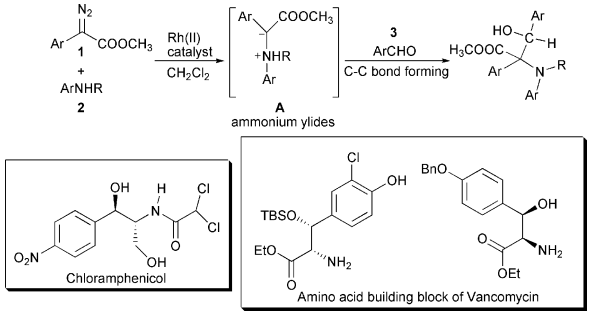
Ammonium ylides generated *in situ* from α-diazo esters and amines in the presence of catalytic $Rh_2(OAc)_4$, undergo an aldol-type reaction with aldehydes affording highly substituted amino acid frameworks in a convergent, three-component reaction.

The chemistry of onium ylides is an area of continuing interest. Phosphorus, sulfur, ammonium and oxonium ylides have been widely utilized in organic synthesis.[1] In the study of ammonium ylides derived from metal carbenoids, the [2,3]-sigmatropic[2] and [1,2]-Stevens rearrangements[3] have been shown to be powerful strategies for the synthesis of nitrogen heterocycles. To the best of our knowledge, except for our report that ammonium ylides react with imines through nucleophilic addition to afford 1,2-diamines with high diastereoselectivity,[4] no further results have been reported on this aldol-type carbon–carbon bond formation from ylides.[5–7] In this paper we report an aldol-type C–C bond-formation reaction of ammonium ylides with arylaldehydes.

The demand for more efficient ways to construct complex chemical structure from simple, readily available precursors continues unabated. Their inherent atom efficiency and ease of implementation has driven the resurgence of interest in multi-component reactions.[8] In a continuation of our interest in multicomponent reactions of ammonium ylides generated from intermolecular trapping of a metal carbenoid by amine, we now describe a novel three-component reaction of rhodium(II) acetate-catalyzed diazo decomposition of phenyldiazoacetate in the presence of an arylamine and an arylaldehyde for the synthesis of densely functionalized β-aryl-β-hydroxy α-amino acid frameworks. Such a framework is a subclass of β-hydroxy α-amino acids carrying an aromatic substituent at the β-position, which are of special interest as they are a key constituent of peptide antibiotics, such as chloramphenicol and vancomycin (Scheme 1).[9]

From the outset of this study, we designed a one-pot reaction of phenyldiazoacetate **1a**, aniline **2a**, and arylaldehyde **3a–c** in the presence of $Rh_2(OAc)_4$ (Table 1). During the course of investigation, neither epoxidation with aldehydes **3** nor aziridination with imines was observed.[10,6d] Only the three-component C–C bond-formation products **5** generated from ammonium ylides (**A**, Scheme 1) were obtained in competition with N–H insertion product **4**.



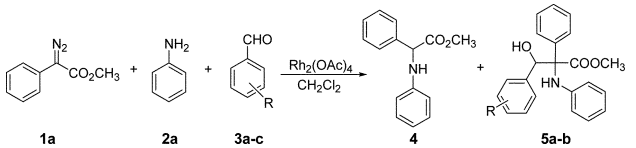
Scheme 1

In contrast to moderate yield enhancement of **5** by using a 3 equiv excess of aldehydes (entries 2 *vs.* 1 and 4 *vs.* 3, Table 1), introducing an electron-withdrawing substituent to the arylaldehyde remarkably improved the yield of **5** and suppressed N–H insertion (entry 1 *vs.* 3 and 2 *vs.* 4, Table 1). Whereas only trace amount of C–C bonded formation product **5c** was afforded with electron-rich anisaldehyde (entry 5 in Table 1). The results are in consistent with the formation of **5** through an aldol-type addition of ammonium ylide **A** to aldehydes, as shown in Scheme 1, since aldehydes bearing electron-withdrawing groups should have higher reactivity towards nucleophiles.[11] The stereoselectivities of **5** were poor to moderate in this reaction. Isomers of **5** were separated by flash silica gel column chromatography.

Because the outcome of this reaction was critically dependent on the electronic features of sustrates, our further studies concentrated on the behaviour of the ammonium ylides generated *in situ* from substituted diazo compounds **1a–c** and anilines **2a–g** with varing electronic properties. Results shown in Table 2 enforce the sensitivity of the reaction on electronic effect of the substrates.

The reaction proceeded well with electron-donating groups on the phenyl ring of phenyldiazoacetate and arylamine (entries 9, 10, 11 in Table 2). Notably, when 2-anisidine **2c**, 4-methoxyphenyl-diazoacetate **1b** and 4-nitrobenzaldehyde **3b** were used, the reaction gave almost entirely C–C bonded product **5l** with 65% isolated yield (entry 11 in Table 2). Electron-withdrawing groups attached to the ammonium ylides decreased the ratio of desired C–C bonded products to those from N–H insertion (entries 4–7, 13 in Table 2).

Table 1 Three-component reaction of rhodium(II) acetate catalyzed diazo decomposition of phenyldiazoacetate (**1a**) in the presence of aniline (**2a**) and arylaldehydes (**3**)[a]



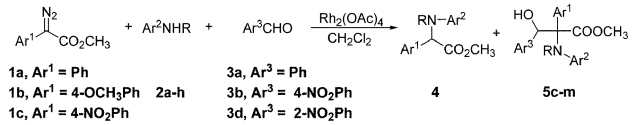
Entry	R	Yield of **5** (%)[b]	**5** : **4**[c]	Isomer ratio of **5**[c] threo : erythro
1	4-NO_2 (**3b**)	74 (**5b**)	79 : 21	52 : 48
2[d]	4-NO_2 (**3b**)	91 (**5b**)	91 : 9	47 : 53
3	H (**3a**)	19 (**5a**)	23 : 77	30 : 70
4[d]	H (**3a**)	26 (**5a**)	31 : 67	32 : 68
5[d]	4-OCH_3 (**3c**)	trace	< 5 : 95	N.d.

[a] Reaction conditions: to a refluxing CH_2Cl_2 mixture of aniline (**2a**, 1.1 equiv), arylaldehydes (**3**, 1.1 equiv) and $Rh_2(OAc)_4$ (0.01 equiv) was added phenyldiazoacetate (**1a**, 1.0 equiv) in CH_2Cl_2 *via* syringe pump over 1 h. [b] Isolated yield after column chromatography purification. [c] Determined by ^1H NMR from crude reaction mixture. [d] 3 equiv of arylaldehyde was used.

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b4/b407449a/

DOI: 10.1039/b407449a

Table 2 Three-component reaction of rhodium(II) acetate catalyzed diazo decomposition of phenyldiazoacetate in the presence of anilines and arylaldehydes[a]



Entry	Diazo ester	Ar^2NHR	Ar^3CHO	**5** : **4**[c]	Yield[b] (%) Product (**5c–m**)	Isomer ratio of **5**[c] Threo : erythro
1	**1a**	4-OCH_3Ph (**2b**)	**3b**	70 : 30	56 (**5c**)	64 : 36
2	**1a**	2-OCH_3Ph (**2c**)	**3b**	84 : 16	74 (**5d**)	46 : 54
3	**1a**	2-OCH_3Ph (**2c**)	**3d**	59 : 41	56 (**5e**)	42 : 58
4	**1a**	4-ClPh (**2d**)	**3b**	68 : 32	58 (**5f**)	49 : 51
5	**1a**	4-CF_3Ph (**2e**)	**3b**	66 : 34	52 (**5g**)	67 : 33
6	**1a**	4-NO_2Ph (**2f**)	**3b**	68 : 32	54 (**5h**)	45 : 55
7	**1a**	2,4-$(NO_2)_2$Ph (**2g**)	**3b**	0 : 100	—	—
8	**1a**	$PhNHCH_3$ (**2h**)	**3b**	7 : 93	<5 (**5i**)	—
9	**1b**	Ph (**2a**)	**3a**	44 : 56	28 (**5j**)	38 : 62
10	**1b**	Ph (**2a**)	**3b**	89 : 11	86 (**5k**)	44 : 56
11	**1b**	2-OCH_3Ph (**2c**)	**3b**	96 : 4	65 (**5l**)	47 : 53
12	**1b**	4-NO_2Ph (**2f**)	**3b**	52 : 48	40 (**5m**)	37 : 63
13	**1c**	Ph (**2a**)	**3b**	0 : 100	—	—

[a] Reaction conditions: same as Table 1. [b] Same as in Table 1. [c] Same as in Table 1.

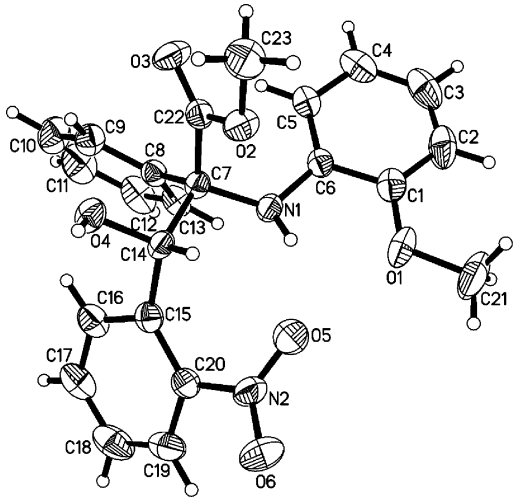
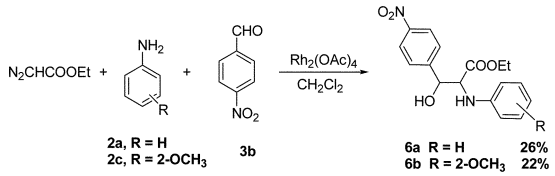


Fig. 1 X-ray structure of erythro-**5e**.

Diazo decomposition of 4-nitrophenyldiazoacetate gave exclusively N–H insertion product (entry 13 in Table 2) and the use of *N*-methylaniline produced a dramatic decrease of the desired product yield (entry 8 in Table 2). This results revealed that electron rich ylides produced more C–C bond-formation product, and therefore were consistent with the reaction pathway in which **5** is formed *via* an nucleophilic addition of the ylide to the aldehyde.

The structural assignment of β-aryl-β-hydroxy α-amino acids **5** and its stereochemistry was unambiguously confirmed by single crystal X-ray structure of erythro-**5e** (Fig. 1).[12]

For future synthetic endeavors, a preliminary study of the scope of this reaction was undertaken. Other α-diazocarbonyl compounds were utilized in the reaction. Reaction of commercially available ethyl diazoacetate, aniline **2a** or **2c** and 3 equiv 4-nitroaldehyde **3b** in the presence of 1 mol% $Rh_2(OAc)_4$ afforded desired C–C bonded product **6a** or **6b** in 26 and 22% yield, respectively, after column chromatography purification (Scheme 2). However, the use of diazomalonate only gave the



Scheme 2

N–H insertion product. Further studies to explore various diazo compounds in this reaction are now in progress.

In conclusion, ammonium ylides generated *in situ* from α-diazo esters and anilines in the presence of $Rh_2(OAc)_4$ underwent aldol-type C–C bond-formation reaction with aldehydes to afford an β-aryl-β-hydroxy α-amino acid framework in a one-pot fashion. Our current efforts are focusing on the exploration of the analogous three-component reaction based on ammonium ylides with matched electrophiles.

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11 A plausible mechanism was provided in ref. 4.

12 *Crystal data* for **5e** (erythro): $C_{23}H_{22}N_2O_6$, M_w = 422.43, orthorhombic, space group *Pbca*, a = 9.919(2), b = 16.766(4), c = 25.021(5) Å, V = 4161.9(13) Å^3, Z = 8, T = 291(2) K, μ(Mo Kα) = 0.099 mm^{-1}. Data for the structure were collected on a Siemens P-4X four-circle diffractometer. Intensity measurements were performed on a crystal (dimensions 0.58 × 0.40 × 0.18 mm) in the range 3.26 < 2θ < 52.00°. Of the 4870 measured reflections, 4088 were independent (R_{int} = 0.0151). The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares on F^2. The final refinements converged at R_1 = 0.0470 for $I > 2\sigma(I)$, wR_2 = 0.0998 for all data. The final difference Fourier synthesis gave a min/max residual electron density −0.187/+0.202 e Å^{-3}. CCDC 211232. See http://www.rsc.org/suppdata/cc/b4/b407449a/ for crystallographic data in .cif or other electronic format.