ORGANIC LETTERS

2003
Vol. 5, No. 21
3923−3926

A Novel Three-Component Reaction Catalyzed by Dirhodium(II) Acetate: Decomposition of Phenyldiazoacetate with Arylamine and Imine for Highly Diastereoselective Synthesis of 1,2-Diamines

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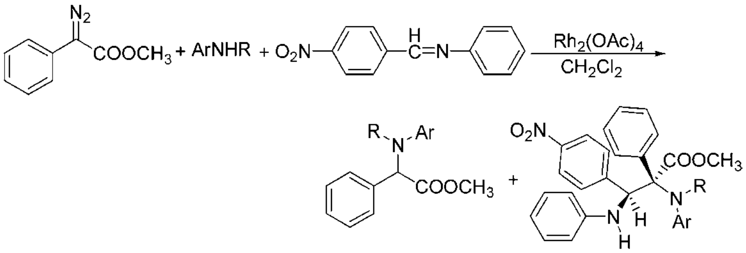
Received August 7, 2003

ABSTRACT



A practical highly diastereoselective synthesis of 1,2-diamines through carbon–carbon bond formation involving an ammonium ylide intermediate is reported for the first time. By treating methyl phenyldiazoacetate with arylamine and imine in the presence of dirhodium acetate, the erythro diastereomer of methyl 1,2-diaryl-1,2-diaminopropanoate is formed with stereochemical preferences greater than 10:1.

Metal-mediated carbenoid reactions have gained wide application in synthetic organic chemistry in the past decades.[1] Many studies of such reactions have focused on cyclopropanation, X−H (X = C, N, O, Si, S) insertion, and ylide generation, and these reactions have also been used to prepare complex synthetic targets.[2] Here we report a novel three-component reaction of rhodium(II) acetate catalyzed diazo decomposition of phenyldiazoacetate in the presence of arylamine and imine.

Rhodium(II) acetate catalyzed diazo decomposition of diazoacetates with imines or amines to give aziridine or N−H insertion product, respectively, have been reported.[1] Recently two methodologies for aziridine formation from diazoacetates through ylide intermediates have been described. We reported stereospecific ring closure of phenyldiazoacetate-derived immonium ylide to form (*E*)-aziridines stereospecifically and in high yields (Scheme 1).[3] Aggarwal developed an alternative pathway for aziridine formation whereby an organic

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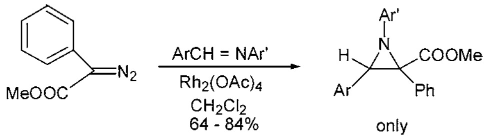
[1] Doyle, M. P.; McKervey, M. A.; Ye, T. *Modem Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley and Sons: New York, 1998.

[2] Padwa, A.; Hornbuckle, S. *Chem. Rev.* **1991**, *91*, 263.

[3] Doyle, M. P.; Hu, W.; Timmons D. J. *Org. Lett.* **2001**, *3*, 933.

10.1021/ol035490p CCC: $25.00

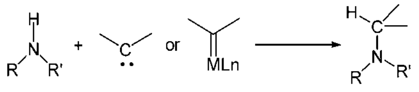
Scheme 1



sulfide intercepts the metal carbene, and aziridination takes place via nucleophilic addition of a sulfur ylide to an imine.[4,5]

The insertion of a metal carbenoid generated from a diazo compound into an N−H bond, which leads to C−N bond formation (Scheme 2), is a known process.[1,6] There have been numerous demonstrations of the versatility of this reaction. For example, this approach has been particularly fruitful in the synthesis of penicillins and related β-lactams.[7]

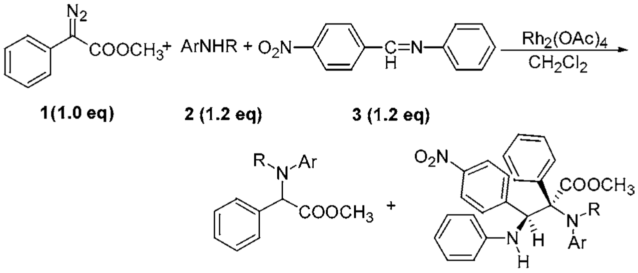
Scheme 2



A novel three-component reaction is reported here. By reaction of phenyldiazoacetate with both imine and amine in the presence of dirhodium acetate catalyst, no aziridine product is obtained. Instead, we find a 1,2-diamine product. For example, treatment of phenyldiazoacetate **1** with a mixture of equal amounts of arylamine **2** and imine **3** with dirhodium acetate catalyst gives N−H insertion product **4** and 1,2-diamines **5**[8] in good yield (Table 1). While the product ratio is dependent on electronic features from aryl substitution of the corresponding amine (Table 1), diastereoselectivity of **5** is consistently high.

As seen from Table 1, the more electron withdrawing is the substituent attached to the arylamine, the higher is the ratio of diamines product **5** over N−H insertion **4** (Table 1, entries c, d, and e). The structure and relative configuration of major diastereomer **5a** was confirmed by single-crystal X-ray analysis to be erythro (Figure 1).[9]

Table 1. Three-Component Reaction of Methyl Phenyldiazoacetate with Aniline and Imine Catalyzed by Dirhodium(II) Acetate



1(1.0 eq) **2** (1.2 eq) **3** (1.2 eq)

4 **5**

entry	Ar	R	yield,[a] %	**4**:**5**[b]	isomer ratio of **5**[b] threo:erythro
a	C_6H_5	H	68	60:40	9:91
b	p-FC_6H_4	H	72	64:36	6:94
c	p-ClC_6H_4	H	76	54:46	4:96
d	p-$CF_3C_6H_4$	H	72	31:69	4:96
e	p-$NO_2C_6H_4$	H	58	14:86	4:96

[a] Isolated yield of **4** + **5** after column chromatography purification. [b] Determined by ^{1}H NMR of crude product.

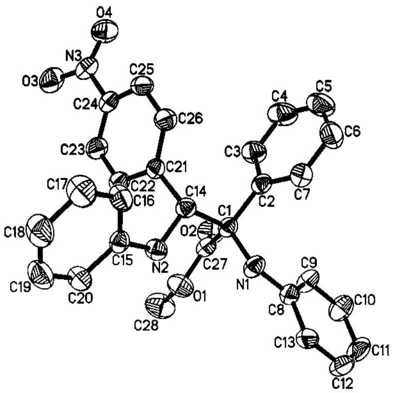


Figure 1. X-ray structure of *erythro*-**5a**.

Further investigation revealed that the concentration of imine was an important factor for driving the reaction to diamine formation (Table 2). As expected from such a competitive process, increasing the initial concentration of

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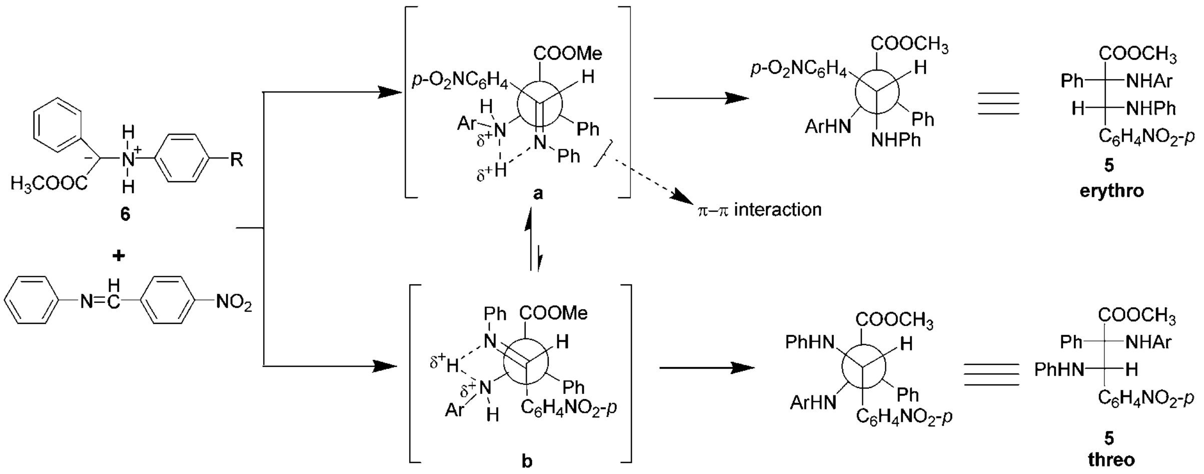
(9) (a) Crystal data for **5a**(erythro): $C_{28}H_{25}N_3O_4$, MW = 467.51, orthorhombic, space group $Pna2(1)$, $a = 26.465(5)$ Å, $b = 9.181(1)$ Å, $c = 9.973(2)$ Å, $V = 2423.2(9)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.281$ Mg/m^3, $F(000) = 984$, $\lambda = 0.71073$ Å, $T = 296(2)$ K, μ(Mo Kα) = 0.087 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 × 0.56 × 0.30 mm) in the range $3.08 < 2\theta < 55.98°$. Of the 3568 measured reflections, 3077 were independent ($R_{int} = 0.0087$). The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares on F^2. The final refinements converged at $R1 = 0.0366$ for $I > 2\sigma(I)$, $wR2 = 0.0720$ for all data. The final difference Fourier synthesis gave a min/max residual electron density of −0.126/+0.139 eÅ^{-3}. (b) CCDC-211231 contains the supplementary crystallographic data for this paper. These data

Scheme 3. A Plausible Mechanism for 1,2-Diamine Formation (Pathway B)



imine results in higher yields of the 1,2-diamine products. For example, the ratio of **5d**/**4d** increased from 69:31 to 92:8 when the molar ratio of **3**/**1** increased from 1.2 to 6. No further change occurred in this ratio with even higher imine concentration.

Table 2. The Effect of Imine Concentration on Yield and Product Ratio of the Three-Component Reaction of **1**, **2d**, and **3** Catalyzed by Rhodium(II) Acetate

$$\mathbf{1} + \mathbf{2d} + \mathbf{3} \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{reflux, 1h}]{\text{Rh}_2(\text{OAc})_4} \mathbf{4d} + \mathbf{5d}$$

entry	molar ratio[a] 3/1	yield,[b] %	**4d**:**5d**[c]	isomer ratio of **5d**[c] threo:erythro
1	1.2	72	31:69	4:96
2	2	75	19:81	7:93
3	4	80	14:86	7:93
4	6	82	8:92	7:93
5	10	85	8:92	8:92

[a] Molar ratio of **2d**/**1** is 1.2. [b] Isolated yield of **4d** + **5d** after purification. [c] Determined by ^{1}H NMR.

The optimized conditions (Table 2, entry 4) were applied to a series of reactions, and the results are summarized in Table 3. In all cases with aniline, 1,2-diamines **5** were the dominant products. However, the use of *N*-methylaniline produced a dramatic decrease in the yield of diamines (Table 3, entry g), but exceptionally high diastereoselecitvity. It is worth noting that carbene dimer formation was observed when 2,4-dinitroaniline, but not any of the other anilines, was used (Table 3, entry f).

Although detailed mechanistic studies have not been undertaken, a plausible mechanism for this three-component reaction is proposed. The existence of dimer when using electron-deficient 2,4-dinitroaniline indicates a slow process. Adding to this that no aziridine was formed even with higher imine concentration, the key intermediate is likely to be ammonium ylide **6**[1,11] (Scheme 3). The reaction can be considered to proceed via initial formation of ammonium ylide **6**, which then undergoes product formation through two competitive reaction pathways: (A) a [1,2]-hydrogen shift[12] to give the N−H insertion product **4** and (B) nucleophilic addition to imine through a concerted five-membered ring transition state to give the observed 1,2-diamines **5**.

Table 3. Three-Component Reaction of Dirhodium(II) Acetate Catalyzed Diazo Decomposition of Phenyldiazoacetate with Arylamines and Imine under Optimized Conditions[a]

$$\mathbf{1} + \mathbf{2} + \mathbf{3} \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{reflux, 1h}]{\text{Rh}_2(\text{OAc})_4} \mathbf{4} + \mathbf{5}$$

entry	Ar	R	yield,[b] %	**4**:**5**[c]	isomer ratio of **5**[c] threo:erythro
a	C_6H_5	H	92	28:72	12:88
b	*p*- FC_6H_4	H	87	30:70	9:91
c	*p*-ClC_6H_4	H	84	18:82	9:91
d	*p*-$CF_3C_6H_4$	H	82	8:92	7:93
e	*p*-$NO_2C_6H_4$	H	82	4:96	15:85
f	2,4-$(NO_2)_2C_6H_4$	H	79	4:96[10]	6:94
g	C_6H_5	CH_3	60	87:13	<3:97[d]

[a] **1**/**2**/**3** = 1:1.2:6. [b] Isolated yield of **4** + **5**. [c] Determined by ^{1}H NMR. [d] Only one isomer was detected by ^{1}H NMR.

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can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

(10) A minor byproduct mixed with **4f** was also isolated but not fully characterized. Identification of the structure of the byproduct is now in progress.

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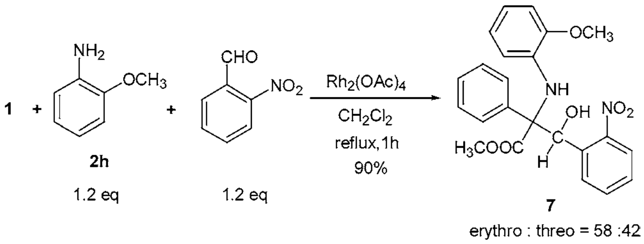
(12) For examples of [l,2]-Stevens rearrangement of ammonium ylides derived from metal carbenoids, see: (a) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, *115*, 1177. (b) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420.

This competition pathway is influenced by the stability of ammonium ylide **6**. The more stable ammonium ylide from the anilines with electron-donating substituents favors formal N−H insertion (pathway A) whereas the less stable ylide from anilines with electron-withdrawing substituents favors formation of the 1,2-diamine product (pathway B). For example, the use of *N*-methylaniline gave mainly the N−H insertion product, while 1,2-diamine was the exclusive product with *p*-nitroaniline. Assuming an approach of the ammonium ylide to the imine, two transition states **a** and **b** lead to the erythro- and threo-diamines, respectively. In both transition states, addition to the imine is activated by intramolecular hydrogen bonding through a five-membered ring. However, in transition states **a**, an additional $\pi-\pi$ interaction between two phenyl groups accounts for the nearly exclusive formation of *erythro*-**5**.

The nucleophilicity of this ammonium ylide was further studied by examining the process with an aromatic aldehyde. Methyl phenyldiazoacetate treated with an equal amount of *O*-anisidine **2h** and 2-nitrobenzaldehyde gave 1,2-amino alcohols[13] **7** in 90% yield (Scheme 4).[14] The poor diastereoselectivity (erythro:threo = 58:42) was not surprising in light of the mechanism proposed for diamine formation (Scheme 3). The energy difference between the two transition states **a** and **b** with aldehyde instead of imine could be negligible due to lack of $\pi-\pi$ interaction with the aldehyde alternative. The structure and configuration of the major diastereomer, *erythro*-**7**, was ascertained by single-crystal X-ray analysis. A detailed study with aldehydes will be reported in due course.

Scheme 4



In conclusion, we have discovered a novel three-component reaction for the preparation of 1,2-diamines with high diastereoselectivity. To our knowledge, this is the first report of C−C bond formation in which ammonium ylides could be trapped by imines or an aldehyde. Further investgations to explore the reactivity of other ammonium ylides and reactions with aldehydes and other electronphiles are in progress.

Acknowledgment. We are grateful for financial support from the Chinese Academy of Sciences and the National Science Foundation of China (Grant No. 20202011). We thank Prof. Kaibei Yu of Chengdu Institute of Organic Chemistry for X-ray measurement. M.P.D. is grateful to the U.S. National Science Foundation and National Institutes of Health for their support.

Supporting Information Available: Experimental procedures and product analyses, as well as crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Reaction of methyl phenyldiazoacetate with aromatic aldehydes alone in the presence of dirhodium catalyst gave only expoxides, see: (a) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 933. (b) Davies, H. M. L.; DeMeese, J. *Tetrahedron Lett.* **2001**, *42*, 6803.