Multicomponent Reactions

DOI: 10.1002/anie.200604389

Efficient Trapping of Oxonium Ylides with Imines: A Highly Diastereoselective Three-Component Reaction for the Synthesis of β-Amino-α-hydroxyesters with Quaternary Stereocenters**

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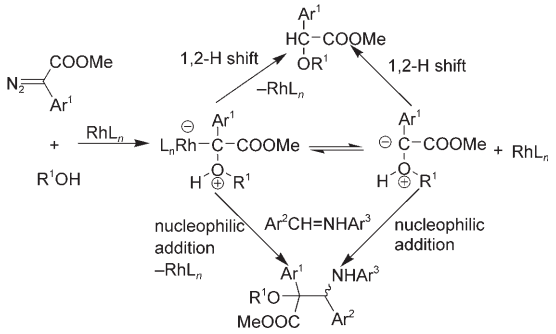
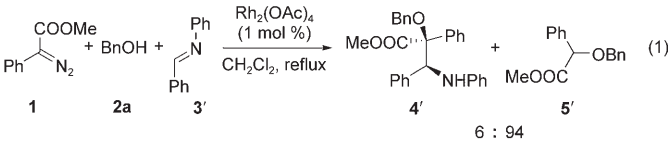
Multicomponent reactions are among the most efficient synthetic methods for the construction of organic molecules.[1] This strategy offers significant advantages over classical step-by-step approaches, as it allows the formation of several bonds in a single synthetic operation. Furthermore, in this way complex molecular architectures can be built up from simple precursors without the need for the isolation of intermediates.

The chemistry of oxonium ylides is an area of continuing interest. For example, carbonyl, phosphorus, sulfur, oxonium, and ammonium ylides have been widely studied and utilized in organic synthesis.[2–6] Recently, we reported a new type of three-component reaction in which ammonium or oxonium ylides generated in situ from diazo compounds with amines or alcohols underwent nucleophilic addition to aldehydes or imines.[7] The reaction afforded highly substituted amino acid frameworks with quaternary stereocenters in one step. β-Amino-α-hydroxy acid derivatives with quaternary stereocenters were obtained from the addition of oxonium ylides to imines. The proposed reaction pathway is shown in Scheme 1. The oxonium ylide generated in situ from a rhodium carbenoid and an alcohol was trapped by an imine to give a Mannich-type addition product. In no case did we find the product of a two-component reaction between the diazo compound and the imine to form an aziridine, but O–H insertion did compete with the desired three-component reaction.

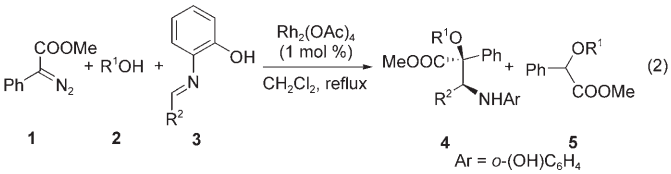
Several issues associated with the reaction limited its application. The reaction occurred with low chemoselectivity and moderate diastereoselectivity, and the range of possible substrates was narrow.[7c] For example, imine **3′** derived from aniline and benzaldehyde gave the O–H insertion product **5** as the major product [Eq. (1)].



Scheme 1. Proposed pathway of the C–C bond-forming reaction of oxonium ylides with imines.



We believed that if the proposed reaction pathway shown in Scheme 1 was correct we should be able to improve the chemoselectivity of the reaction by increasing the electrophilicity of the imine so that it would trap the oxonium ylide more efficiently. Herein we report our recent breakthrough in this approach. By using imines **3** derived from 2-aminophenol, high chemoselectivity and excellent diastereoselectivity were observed together with broad substrate scope [Eq. (2)]. The



imines **3a–e** were thought to be more active electrophilic substrates than **3′** as a result of activation by the phenol functionality through an intramolecular hydrogen bond.

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[**] We are grateful for financial support from the Chinese Academy of Sciences and the National Science Foundation of China (grant no. 20472080). We thank Prof. Kaibei Yu of Chengdu Institute of Organic Chemistry for X-ray measurements. We thank Allychem Co. for providing us with (*R*)-*tert*-butylsulfinamide.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

We conducted an initial reaction with one equivalent each of methyl phenyldiazoacetate (**1**), benzyl alcohol (**2a**), and imine **3a** (Table 1, entry 1) and obtained the three-component product **4a** as the major product with d.r. 97:3. This high diastereoselectivity was found to be quite general for the different alcohols employed (Table 1, entries 2–5). The chemoselectivity was improved to 94:6 in favor of the desired three-component product when the benzylic alcohol used had an electron-withdrawing *p*-nitro substituent (Table 1, entry 5). The reaction with *p*-nitrobenzyl alcohol was then extended to other imines. High chemoselectivity and excellent diastereoselectivity were observed in most cases regardless of the electronic effect of substituents on the imine (Table 1, entries 5–9). The reaction of the electron-poor imine **3e** occurred with relatively low chemoselectivity (**4**/**5** = 88:12). It was interesting to find that the temperature had a significant effect on the chemoselectivity: It was improved to 95:5 simply by decreasing the reaction temperature to 25 °C (Table 1, entry 10).

Table 1: The reaction of methyl phenyldiazoacetate with alcohols and imines **3** [Eq. (2)].[a]

Entry	R^1 (**2**)	R^2 (**3**)	Yield [%][b]	**4**/**5**[c]	d.r. of **4**[c,d]
1	$C_6H_5CH_2$ (**2a**)	C_6H_5 (**3a**)	75 (**4a**)	80:20	97:3
2	Me	C_6H_5 (**3a**)	74 (**4b**)	78:22	>98:2
3	*i*Pr	C_6H_5 (**3a**)	60 (**4c**)	80:20	>98:2
4	*p*-(MeO)$C_6H_4CH_2$	C_6H_5 (**3a**)	64 (**4d**)	74:26	94:6
5	*p*-(NO_2)$C_6H_4CH_2$	C_6H_5 (**3a**)	78 (**4e**)	94:6	97:3
6	*p*-(NO_2)$C_6H_4CH_2$	*p*-(MeO)C_6H_4 (**3b**)	72 (**4f**)	95:5	95:5
7	*p*-(NO_2)$C_6H_4CH_2$	*p*-(CN)C_6H_4 (**3c**)	75 (**4g**)	94:6	>98:2
8	*p*-(NO_2)$C_6H_4CH_2$	1-naphthyl (**3d**)	71 (**4h**)	91:9	>98:2
9	*p*-(NO_2)$C_6H_4CH_2$	*p*-(NO_2)C_6H_4 (**3e**)	67 (**4i**)	88:12	98:2
10[e]	*p*-(NO_2)$C_6H_4CH_2$	*p*-(NO_2)C_6H_4 (**3e**)	75 (**4i**)	95:5	98:2

[a] All reactions were carried out in CH_2Cl_2 at reflux in the presence of $Rh_2(OAc)_4$ (1 mol%). [b] Yield of **4** after chromatography. [c] The ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] The major isomer is *erythro*; see the Supporting Information. [e] The reaction was carried out at 25 °C.

Optically active β-aminoalcohol and β-amino-α-hydroxy acid moieties are found in a large variety of biologically important compounds and natural products[8] as well as in a growing number of ligands and chiral auxiliaries for asymmetric synthesis.[9] However, the asymmetric synthesis of quaternary amino acid derivatives is a difficult and challenging task for organic chemists.[10] As a result of our continuing interest in new synthetic strategies for chiral targets, we found that this method can be extended to the preparation of β-amino-α-hydroxy acid derivatives with a quaternary stereocenter with high optical purity [Eq. (3)].

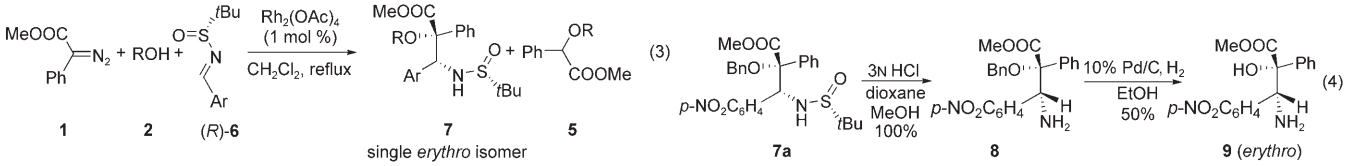
N-(*tert*-butylsulfinyl)imines[11] **6** have been widely used as chiral auxiliaries for the preparation of optically active amines. When chiral imines (*R*)-**6** were used in the reaction, exceptionally high diastereoselectivity was observed. In each case, no other diastereomer of the β-amino-α-hydroxy acid derivative **7** was detected by ^{1}H NMR spectroscopy in the crude reaction mixture (Table 2). The reaction was relatively clean, and the O–H insertion product (**5**) was the only side product formed. An excess of the diazo compound and the alcohol was used to maximize the yield of **7**. The use of benzylic alcohols with electron-withdrawing and electron-donating substituents led to a slight decrease in yield (Table 2, entries 3 and 4). The highest yield of product **7** was observed with ethanol as the alcohol (**7f**; Table 2, entry 6). Compounds **7** were also obtained in moderate to good yield when other alcohols were used in the reaction (Table 2, entries 5, 7, and 8). Although the reaction is currently limited to the use of electron-deficient *N*-(*tert*-butylsulfinyl)imines, our results show the potential of this method for the efficient construction of polyfunctionalized chiral molecules. The structure of **7b** was confirmed by single-crystal X-ray analysis to be the enantiomer shown in Figure 1 with the absolute configuration *R*,*R*,*R*, which indicates that the three-component product is the *erythro* isomer.[12]

Table 2: The reaction of methyl phenyldiazoacetate with alcohols and imines **6** [Eq. (3)].[a]

Entry	R (**2**)	Ar (**6**)	Yield [%][b]	d.r. of **7**[c]
1	$C_6H_5CH_2$ (**2a**)	*p*-(NO_2)C_6H_4 (**6a**)	58 (**7a**)	>98:2
2	$C_6H_5CH_2$ (**2a**)	2,4-(NO_2)$_2C_6H_3$ (**6b**)	42 (**7b**)	>98:2
3	*p*-(MeO)$C_6H_4CH_2$	*p*-(NO_2)C_6H_4 (**6a**)	40 (**7c**)	>98:2
4	*p*-(NO_2)$C_6H_4CH_2$	*p*-(NO_2)C_6H_4 (**6a**)	38 (**7d**)	>98:2
5	Me	*p*-(NO_2)C_6H_4 (**6a**)	45 (**7e**)	>98:2
6	Et	*p*-(NO_2)C_6H_4 (**6a**)	62 (**7f**)	>98:2
7	*i*Pr	*p*-(NO_2)C_6H_4 (**6a**)	35 (**7g**)	>98:2
8	$H_2C{=}CHCH_2$	*p*-(NO_2)C_6H_4 (**6a**)	50 (**7h**)	>98:2

[a] All reactions were carried out in CH_2Cl_2 at reflux in the presence of $Rh_2(OAc)_4$ (1 mol%). [b] Yield of **7** (based on the imine **6**) after chromatography. [c] The ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture; only the *erythro* isomer was observed.

The *N*-sulfinyl protecting group was removed readily from product **7a** under mild conditions [Eq. (4)].[13] The treatment of **7a** with HCl gave **8** quantitatively with 98% *ee*. The benzyl group was removed by hydrogenolysis under nonoptimized reaction conditions to give the free β-amino-α-hydroxyester **9** in 50% yield.



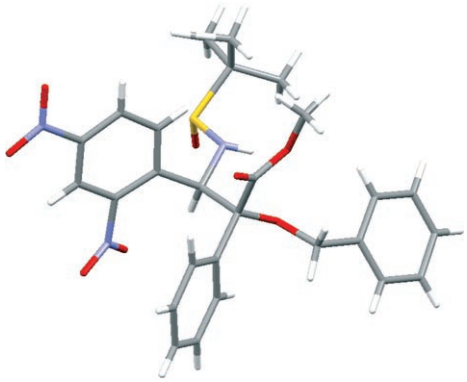


Figure 1. X-ray crystal structure of (*R*,*R*,*R*)-**7b**.

In conclusion, we have developed a process for the efficient trapping by imines **3** and **6** of oxonium ylides generated in situ from phenyldiazoacetates and alcohols. Excellent diastereoselectivity was observed in this three-component reaction. The use of *N*-(*tert*-butylsulfinyl)imines **6** provides ready access to β-amino-α-hydroxyesters of high optical purity through the construction of quaternary stereocenters by C–O and C–C bond formation in a single step. Further investigations on the application of this methodology are in progress.

Experimental Section

General procedure: A solution of **1** (95 mg, 0.54 mmol) in CH_2Cl_2 (2 mL) was added over 1 h by a syringe pump to a solution of $Rh_2(OAc)_4$ (2.38 mg, 1 mol%), **2a** (56.4 μL, 0.54 mmol), and **3a** (116.0 mg, 0.59 mmol) in CH_2Cl_2 (4 mL) at reflux under an argon atmosphere. When the addition was complete, the reaction mixture was cooled to room temperature, and the solvent was removed. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/light petroleum 1:9) to give **4a** (184 mg, 75%). Products **4b–i** were obtained by the same procedure. Products **7** were obtained by the same procedure with a molar ratio **1**/**2**/**6** of 2:2:1. See the Supporting Information for details.

Received: October 26, 2006
Revised: November 24, 2006
Published online: January 4, 2007

Keywords: carbenes · diazo compounds · imines · multicomponent reactions · ylides

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[12] Crystal data for **7b**: $C_{27}H_{29}N_3O_8S$, $M_r = 555.59$, orthorhombic, space group $P2_12_12_1$, $a = 6.729(1)$, $b = 19.655(5)$, $c = 21.659(5)$ Å, $V = 2864.6(11)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.288$ Mg m^{-3}, $F(000) = 1168$, $\lambda = 0.71073$ Å, $T = 289(2)$ K, $\mu(Mo_{K\alpha}) = 0.165$ mm^{-1}. Data for the crystal structure were collected on a Siemens P-4X four-circle diffractometer. Intensity measurements were performed on a crystal (dimensions 0.56 mm × 0.46 mm × 0.46 mm) in the range $2.8 < 2\theta < 54.0°$. Of the 7641 measured reflections, 6268 were independent ($R_{int} = 0.0194$). The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares techniques on F^2. The final refinements converged at $R_1 = 0.0448$ for $I > 2\sigma(I)$, $wR_2 = 0.0817$ for all data. The final difference Fourier synthesis gave a min/max residual electron density of $-0.174/+0.165$ e Å^{-3}. CCDC-238733 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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