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Scandium triflate catalyzed diazocarbonyl insertions into heteroatom-hydrogen bonds

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Abstract

Scandium triflate is an efficient catalyst for diazocarbonyl insertion reactions into O-H, S-H and carbamate N-H bonds. The O-H and S-H insertion reactions proceed at ambient temperature and selective O-H insertion is possible in the presence of a carbamate N-H. A novel approach to α-amino acids involving intramolecular carbene/N-H insertion as the key step has been demonstrated. © 1999 Elsevier Science Ltd. All rights reserved.

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As part of an ongoing synthetic program we required an efficient route to several α-alkoxy aryl ketones. Structural features of some of the target ketones necessitated the use of mild reaction conditions for their preparation and the approach best suited to our needs appeared to be the carbene/OH insertion reaction of a diazoketone and an alcohol[1]. Herein, we describe preliminary results on the use of scandium triflate[2] as a catalyst for this and other carbene insertion reactions into heteroatom-hydrogen (XH) bonds.

The carbene/XH insertion reaction has been the focus of recent investigations that have examined diazoester/OH insertion reactions as well as diazoester/NH insertions[3,4] employing a variety of catalysts. The use of $RuCl_2(PPh_3)_3$ as an alternative to the traditional $Rh_2(OAc)_4$ in diazoketone insertion reactions was reported recently[5]. To the best of our knowledge $Sc(OTf)_3$ has not been examined as a catalyst for carbene heteroatom-hydrogen bond insertion reactions[6].

Initial investigations were conducted on aryl diazoketones. Treatment of a variety of aryl diazoketones 1 with several alcohols in the presence of $Sc(OTf)_3$ (2-10mol%) at ambient temperature generated the corresponding α-alkoxy ketones 2 as products of OH insertion. The reaction may be conducted in benzene or dichloromethane as solvent and is faster with primary alcohols than with secondary (Scheme 1, Table 1).

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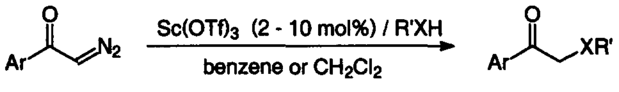

1a - d 2a - i

Scheme 1

Table 1: Sc(OTf)$_3$ catalyzed O-H and S-H insertion reactions of aryl diazoketones

Substrate	Ar	mol% Sc(OTf)$_3$	Product	XR'	Yield %^{a}
1a	4-EtOC$_6$H$_4$	2	2a	OCH(CH$_3$)$_2$	64
1b	Ph	5	2b	SPh	62
	Ph	5	2c	OCH$_2$CH$_2$NHZ^b	30
1c	4-ClC$_6$H$_4$	5	2d	OMe	93
	4-ClC$_6$H$_4$	10	2e	OCH(CH$_3$)Ph	64
1d	2-thiophenyl	10	2f	S(CH$_2$)$_3$CH$_3$	40
	2-thiophenyl	10	2g	SPh	46
	2-thiophenyl	10	2h	OCH$_2$CH$_2$NHZ	36
	2-thiophenyl	3	2i	OCH$_2$Ph	63

a: unoptimized yields b: Z = COOCH$_2$Ph

It is noteworthy that practically all of the previous studies on Brönsted or Lewis acid mediated diazoketone insertion reactions involving heteroatom participation are restricted to the intramolecular mode[7,8] and the present intermolecular version offers an attractive alternative to most of the methods for the synthesis of α-alkoxy aryl ketones[9]. The procedure for the preparation of **2a** is representative.[1] *N*-Benzyloxycarbonyl ethanolamine was also examined as the heteroatom component. Reaction of diazoacetophenone (**1b**) and the thiophene-2-carboxylic acid derived diazoketone **1d** with *N*-Cbz ethanolamine in the presence of Sc(OTf)$_3$ at ambient temperature did generate the O-H insertion products **2c** and **2h** respectively, but in low yield (30% and 36% respectively) indicating that the carbamate functionality may be detrimental to the intermolecular insertion process. However, products arising from competing N-H insertion were not detected. Conducting the reaction at elevated temperature had no beneficial effect. Sc(OTf)$_3$ also catalyzes the carbene/SH insertion reaction to generate the corresponding phenylthio ketones **2b** and **2g** by the reaction of diazoketones **1b** and **1d** with thiophenol at ambient temperature. A similar reaction of **1d** with butanethiol generates **2f** in moderate yield. The results are summarized in Table 1.

We next examined amino acid and hydroxy acid derived diazocarbonyl substrates in the O-H insertion reaction. Treatment of the diazoketone **3** derived from *N*-Cbz-phenylalanine with Sc(OTf)$_3$ in the presence of methanol did not generate any of the required O-H insertion

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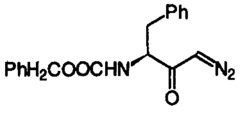
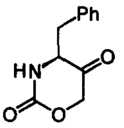
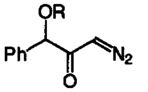
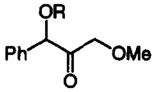
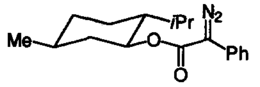
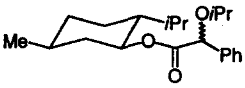
[1] **General procedure for the Sc(OTf)$_3$ catalyzed insertion reaction of diazocarbonyls and alcohols:** To a solution of the diazoketone or diazoester in dichloromethane or benzene was added the appropriate alcohol followed by Sc(OTf)$_3$. The mixture was stirred at ambient temperature till completion of the reaction (TLC). Additional solvent was added and the solution was washed with water and concentrated to give the crude product which was purified by flash chromatography on silica gel.

1-(4-Ethoxyphenyl)-2-(2-propoxy)ethanone (2a): This was prepared by the reaction of 4-ethoxydiazoacetophenone (**1a**) (100 mg, 0.5 mmol) and isopropyl alcohol (26 mmol) in the presence of Sc(OTf)$_3$ (5 mg, 2 mol%) in benzene (2 ml) at ambient temperature for 10 h, to give after purification by flash chromatography on silica gel (petroleum ether/EtOAc 9/1) 75 mg (64%) of **2a**. Data for **2a**: IR (CHCl$_3$): 3020, 1705, 1620, 1230, 1190, 1130, 1050, 770, 690 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.9 (d, *J* = 9, 2H, ArH), 6.9 (d, *J* = 9, 2H, ArH), 4.65 (s, 2H, COC*H*$_2$), 4.1 (q, *J* = 7, 2H, OC*H*$_2$), 3.7 (septet, *J* = 6.5, 1H, C*H*(CH$_3$)$_2$), 1.4 (t, *J* = 7, 3H, C*H*$_3$), 1.2 (d, *J* = 6.5, 6H, CH(C*H*$_3$)$_2$). MS (70 eV): m/z 65 (17), 107 (5), 121 (65), 149 (100), 223 (M+1, (1)). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.29; H, 8.16. Found: C, 70.33; H, 8.26.

product. The major product isolated is **4** (61%) arising from intramolecular reaction of the carbenoid with the *N*-protecting group followed by debenzylation. A similar carbonyl group participation has been observed in the $Rh_2(OAc)_4$ catalyzed decomposition of an oxazolidinone based diazoketone[10]. Studies with mandelic acid derived diazoketones were more successful. Thus, racemic *O*-acetyl mandelic acid was converted to the diazoketone **5a** which generated the methanol insertion product **6a** (40%). Replacement of the acetate with a methyl ether is beneficial and **6b** is obtained in 69% yield from the diazoketone **5b** derived from racemic α-methoxy phenylacetic acid.

Insertion reactions of the menthol derived diazoester **7**[3] were also examined. Reaction of **7** with isopropyl alcohol in the presence of $Sc(OTf)_3$ (1 mol%) is very facile in a variety of solvents and generates the α-isopropoxy ester **8** in excellent yield at ambient temperature but with low diastereoselectivity (ds=1.2/1). These results are summarized in Table 2.

Table 2: $Sc(OTf)_3$ catalyzed O-H insertion reactions of functionalized diazoketones and diazoesters

Substrate	Product	Yield %
 **3**	 **4**	61
 **5a**, R = Ac **5b**, R=Me	 **6a,b**	**6a**, 40 **6b**, 69
 **7**	 **8**	90

Although the $Sc(OTf)_3$ catalyzed intermolecular N-H insertion reaction could not be affected either with a secondary amine (reaction of **1b** and morpholine was unsuccessful) or a carbamate, the intramolecular version is quite successful. The diazoester **9** was prepared from the benzoylformate ester of *N*-Cbz ethanolamine by conversion to the tosyl hydrazone and subsequent treatment with triethylamine (52% overall yield from benzoylformic acid). When a benzene solution of **9** was heated in the presence of $Sc(OTf)_3$ (1 mol%), 3-phenyl-4-benzyloxycarbonyl morpholin-2-one (**10**), the product of intramolecular N-H insertion, was obtained in 63-66% yield.[2] It is noteworthy that **10** is obtained in only 10% yield when

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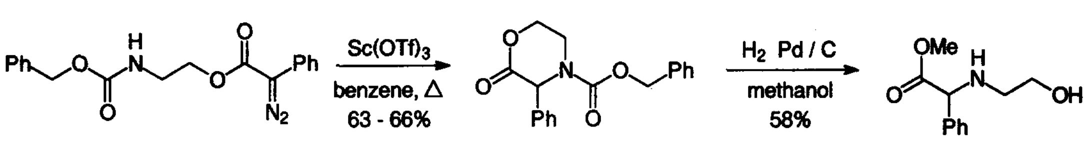
[2] **3-Phenyl-4-benzyloxycarbonyl morpholin-2-one (10)**: To refluxing suspension of $Sc(OTf)_3$ (1.5 mg, 1 mol%) in benzene (0.5 mL) was added dropwise a solution of diazoester **9** (100 mg, 0.3 mmol) in benzene (1 mL). The mixture was heated to reflux for 1 h after which it was concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 3/1) to give 61 mg (66%) of **10** as a colourless gum. Data for **10**: IR (neat): 3080, 3040, 2960, 2900, 1770, 1720, 1610, 1600, 1500, 1460, 1430, 1300, 1220, 1130, 1070, 1040, 1010, 980, 920, 860 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.6-7 (m, 10H, Ar*H*), 6.2-5.75 (br, 1H, PhC*H*), 5.4-4.95 (br, 2H, OCH_2Ph), 4.5-4.1 (br, 2H, OCH_2), 3.95-3.60 (br, 2H, NCH_2). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 166.8, 154.8, 135.8, 135.3 (ArCipso), 129.0, 128.5, 128.3, 127.9, 125.7 (ArC), 68.0 (OCH_2Ph), 64.9 (OCH_2CH_2), 59.6 (PhCH), 40.7 (NCH_2). MS (70 eV): m/z 65 (21), 77 (19), 91 (100), 105 (33), 118 (15), 132 (10), 148 (5), 176 (13), 220 (25), 311 (M^+, 1).

$Rh_2(OAc)_4$ is employed as a catalyst under identical conditions. The observation that no **10** is formed in the absence of any catalyst confirms the catalytic effect of $Sc(OTf)_3$ in the N-H insertion reaction. Hydrogenation of **10** in methanol proceeds with concomitant methanolysis to generate the phenylglycine derivative **11** (58%, unoptimized, Scheme 2).



9 10 11

Scheme 2

The overall conversion of **9** to **11** constitutes a new approach to α-amino acids, based on intramolecular N-H insertion that proceeds with the creation of a stereogenic center. Although the intramolecular carbene/N-H insertion approach works well for the preparation of modified β-lactams and piperidines[1], earlier attempts at this conversion with diazoesters structurally related to **9** have been either low yielding[11] or unsuccessful[12,13]. $Sc(OTf)_3$ thus offers a singular advantage.

In conclusion, $Sc(OTf)_3$ has been demonstrated to be a useful catalyst for diazoketone and diazoester derived carbenoid/heteroatom-hydrogen bond insertion reactions to generate a variety of α-alkoxy, α-phenylthio and α-alkylthio ketones and esters. The $Sc(OTf)_3$ catalyzed intramolecular diazoester N-H insertion reaction offers a new route to α-amino acid derivatives. Current efforts focus on asymmetric modification[14] of these reactions.

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