ChemPubSoc Europe

DOI: 10.1002/ejoc.201600064

EurJOC European Journal of Organic Chemistry

Communication

Diazo, O–H Insertion

$Rh_2(esp)_2$: An Efficient Catalyst for O–H Insertion Reactions of Carboxylic Acids into Acceptor/Acceptor Diazo Compounds

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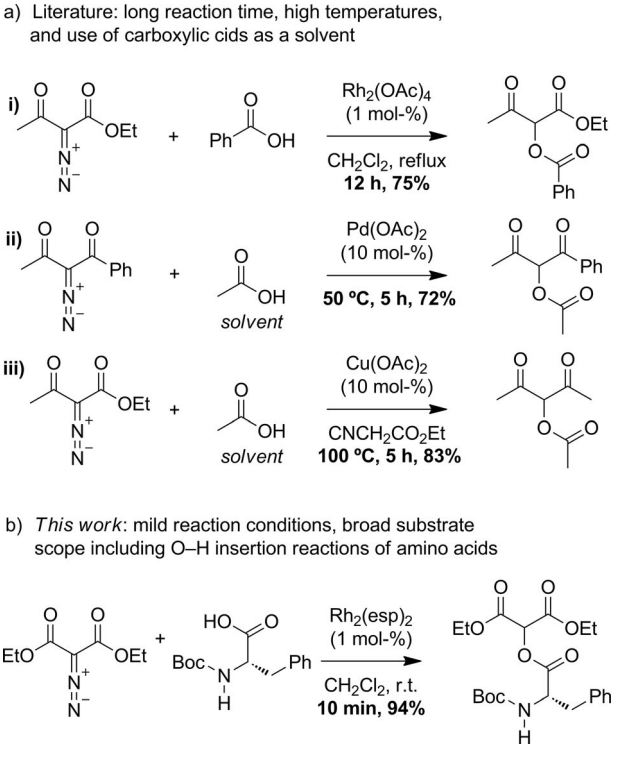
Abstract: $Rh_2(esp)_2$ has been identified as a highly efficient catalyst for O–H insertion of carboxylic acids into acceptor/acceptor diazo compounds. The insertion reaction proceeds in CH_2Cl_2 within minutes at room temperature in excellent yields and accommodates carboxylic acids having varying functionalities including amino acids, free alcoholic and phenolic O–H, indole N–H, alkenes, alkynes, and substituted aromatics. In addition, the reaction tolerates a broad range of stable diazo compounds carrying diverse functional groups.

Introduction

Acceptor/acceptor (A/A) diazo compounds are important building blocks in organic synthesis capable of novel transformations such as cyclopropanation, cyclopropenation, insertion reactions (C–H, N–H, O–H, S–H, B–H), trifluoromethylation, dipolar addition, cascade, and rearrangement reactions.[1] However, A/A diazo compounds, particularly those derived from dicarbonyls, are the most stable diazo reagents.[2] Because of their stability, harsh reaction conditions are required for the extrusion of nitrogen to generate reactive carbene intermediates. These reaction conditions limit the utility of A/A diazos in significant transformations that demand selectivity such as cascade reactions, and access to the α-acyloxy carbonyl motif found in complex molecules and bioactive scaffolds.[3]

O–H insertion reactions of alcohols into diazo compounds have been thoroughly investigated. However, only a few examples of O–H insertion reactions of carboxylic acids into A/A diazo compounds are reported in the literature with Rh^{II}, Pd^{II}, and Cu^{II} salts (Scheme 1, a).[4] The reaction conditions for these transformations require long reaction times, high temperature, and use of carboxylic acids as a solvent.[5] Therefore, these conditions are not suitable for the O–H insertion reaction of carboxylic acids carrying reactive functional groups such as alkene, alkyne, aliphatic- and phenolic-OH, and electron-rich aromatic rings. In particular, there is no example known in the literature for the insertion of amino acids into A/A diazo compounds such as diazodicarbonyls.

Herein, we report a novel $Rh_2(esp)_2$-catalyzed O–H insertion reaction of carboxylic acids into A/A diazo compounds. The reaction proceeds under mild conditions within minutes at room temperature to provide the insertion product in excellent yield (Scheme 1, b).



Scheme 1. O–H insertion reactions of carboxylic acids into acceptor–acceptor diazo compounds.

Results and Discussion

We initiated our work toward identifying an efficient catalyst that would allow the O–H insertion of carboxylic acids into A/A diazo compounds under mild conditions. For the initial optimization, diethyl diazomalonate (**1a**), and Boc-L-Phe-OH (**2a**) were selected as model substrates and exposed to the most efficient conditions known in literature (Table 1, entries 1–5). To our delight, insertion product **3a** was obtained with all the metal(II) salts (Rh/Pd/Cu).[6] Among all insertion reactions, $Rh_2(OAc)_4$ proceeded under mildest conditions in moderate

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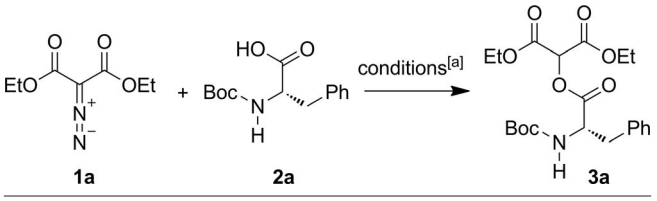
yield (entry 1). Notably, diethyl 2-hydroxymalonate was obtained as the major side product under all these conditions presumably because of competing O–H insertion reaction of water with carboxylic acid.

Table 1. O–H insertion reactions of Boc-L-Phe-OH into diethyl diazomalonate.



Entry	Reagent [a]	Solvent, *T* [°C], *t*	**3**, yield [%][b]
1	$Rh_2(OAc)_4$	CH_2Cl_2, room temp., 12 h	64
2	$Pd(OAc)_2$	CH_2Cl_2, reflux, 8 h	58
3	$Cu(acac)_2$	DCE, reflux, 5 h	62
4	$Cu(OAc)_2$	DCE, reflux, 5 h	43
5	$Cu(OAc)_2$/$CNCH_2CO_2Et$	DCE, reflux, 12 h	55
6	$Rh_2(TFA)_4$[c]	CH_2Cl_2, r.t., 6 h	46
7	$Rh_2(HFB)_4$[d]	CH_2Cl_2, r.t., 6 h	67
8	$Rh_2(esp)_2$	CH_2Cl_2, r.t., 10 min	94
9	–	TFE,[e] reflux, 12 h	n.r.
10	Hoveyda–Grubbs2nd gen.	CH_2Cl_2, reflux, 10 h	40

[a] All optimization reactions were performed with **1a** (1.50 equiv.), **2a** (1 equiv.) and catalyst (1 mol-%). [b] Isolated yields after column chromatography; n.r.: no reaction. [c] TFA = trifluoroacetate. [d] HFB = heptafluorobutyrate. [e] TFE = trifluoroethanol.

Encouraged by these findings, we then screened other Rh^{II} salts that could reduce reaction time and avoid the byproduct resulting from competing O–H insertion of water (entries 6–8). To our surprise, $Rh_2(esp)_2$ developed by the Du Bois group for C–H amination,[7] and also known for O–H insertion reactions of alcohols into diazo compounds,[8] initiated the acid insertion reaction at room temperature within minutes in excellent yield (entry 8).

We also screened other known conditions for decomposition of A/A diazo compounds such as trifluoroethanol (TFE) as a solvent[9] (entry 9) and the Hoveyda–Grubbs (2nd generation) catalyst recently reported by the Hussaini group[10] (entry 10). However, these conditions were met with limited success as evident with no reaction under TFE conditions even under refluxing conditions.

With optimized conditions in hand, we then investigated scope of the $Rh_2(esp)_2$-catalyzed O–H insertion reaction with diethyl diazomalonate and its applicability to a range of amino acids (Figure 1). Sterically hindered amino acids such as Boc-Pro-OH were inserted with high efficiency into diethyl diazomalonate (Figure 1, **3b**). The reaction also proceeded in good yield with Boc-Ser-OH having a free hydroxyl side chain (Figure 1, **3c**) producing only a minimum amount (18 %) of the double insertion product (**S1a**, see Supporting Information for details). The varying electron rich reactive sites of the indole moiety in tryptophan exhibited some challenges, providing the desired product (Figure 1, **3d**) in a relatively lower yield.[11]

To further explore the generality of this transformation, a wide range of carboxylic acids carrying reactive functional groups such as alkene, alkyne, phenolic –OH, and electron-rich/-deficient aromatic rings were examined (Figure 1, **3e**–**m**). To

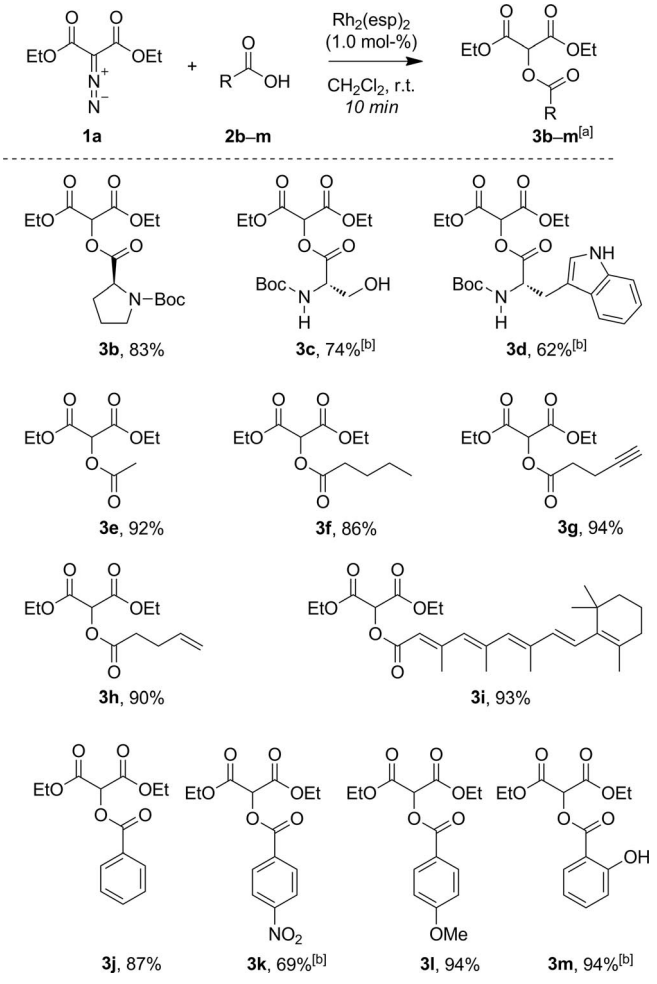


Figure 1. Scope of $Rh_2(esp)_2$-catalyzed room temperature O–H insertion reactions of carboxylic acids. [a] **1a** (1.5 equiv.), **2b**–**m** (1 equiv.). [b] Syringe pump addition of diethyl diazomalonate **1a** over a period of 2–4 h.

our delight, carboxylic acids containing alkyne and alkene functionality afforded the corresponding insertion product (Figure 1, **3g**–**i**) in high yields without any evidence of cyclopropenation or cyclopropanation.

Next, we investigated the electronic effects of aryl substituents on the reactivity of carboxylic acids (Figure 1, **3j**–**3l**). Notably, 4-nitrobenzoic acid (Figure 1, **3k**) was less reactive and required slow addition of diethyl diazomalonate via a syringe pump to avoid decomposition of the A/A diazo without insertion. Conversely, 4-methoxybenzoic acid was highly reactive and provided the insertion product in excellent yield (Figure 1, **3l**).

It is important to note that in the presence of the phenolic –OH found in salicylic acid, the desired carboxylic acid –OH insertion product is obtained in excellent yield, with no production of a bis-inserted side product (Figure 1, **3m**). This finding demonstrates the compatibility of the phenolic O–H side chain in this transformation.[12]

Next, we examined the electronic effects of various electron-withdrawing groups on the reactivity of A/A diazos. All of the diazo substrates carrying varying functionalities were synthesized using literature procedures except compounds **1c** and **1j**.

These compounds were prepared from the corresponding active methylene compounds using 4-acetamidobenzenesulfonyl azide as our diazo-transfer reagent (see Supporting Information for details).

For the substrate scope, the reaction accommodates a broad range of stable diazo compounds having diverse electron-withdrawing functionalities such as esters, amides, and aliphatic carbonyl compounds (Figure 2, **3n**–**q**). We were delighted to find that the highly stabilized 1,3-indandione derived diazo also proceeds smoothly at room temperature to provide the insertion product (Figure 2, **3r**), albeit at a longer reaction time of 3 hours. The developed conditions were also conducive to varying sites of reactivity found within oxindoles, including free NH (Figure 2, **3s**, **3t**). These reaction conditions are not only limited to A/A diazos but also work efficiently with acceptor diazo compounds (Figure 2, **3u**). Lastly, it is important to note the applicability of this transformation to biologically important molecules as evident from the sole carboxylic acid O–H insertion product obtained with diazo-containing phenylalanine (Figure 2, **3v**).

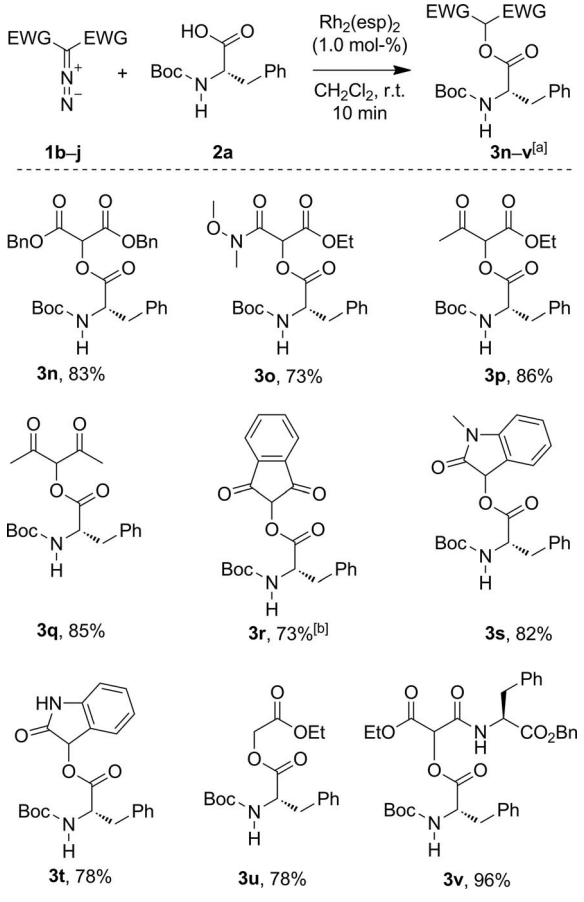


Figure 2. Scope of $Rh_2(esp)_2$-catalyzed room temperature O–H insertion reactions of Boc-L-Phe-OH with diazo compounds carrying varying functionalities. [a] **1b**–**j** (1.5 equiv.), **2a** (1 equiv.), **3o**, **3p**, **3s**, **3t**, and **3v** were obtained as a mixture of inseparable diastereomers (1:1). [b] Reaction time increased to 3 h.

Conclusions

In conclusion, the reported $Rh_2(esp)_2$-catalyzed diazo-acid insertion conditions are mild and selective while also representing the first example of an amino acid insertion into A/A diazos. An important feature of this transformation is the chemoselectivity toward carboxylic acid O–H insertion when molecules possess diazo-reactive functionalities such as alkenes, alkynes, hydroxyl and phenolic O–H, and electron-rich aromatics including indole N–H. This methodology also offers the possibility to perform enantioselective transformations when required given the mild reaction conditions. Applications of this chemoselective O–H insertion reaction to cascade transformations are on going and will be reported in due course.

Acknowledgments

The authors thank Dr. Susan Nimmo and Dr. Steven Foster for expert NMR and mass spectral support, and the University of Oklahoma start-up funds and the Office of the Vice President for Research for generous financial support. We would also like to thank the University of Oklahoma, College of Arts & Sciences for monetary support through the Junior Faculty Fellowship Award to I. S. and the Robberson Research Fellowship to A. H.

Keywords: Homogeneous catalysis · Diazo compounds · Rhodium · O–H Insertion · Chemoselective

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Received: January 17, 2016
Published Online: March 9, 2016

