Communication

Rh(II)-Catalyzed Intermolecular Oxidative Sulfamidation of Aldehydes: A Mild Efficient Synthesis of *N*-Sulfonylcarboxamides

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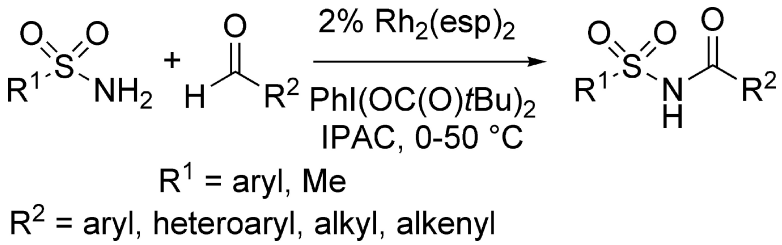

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Rh(II)-Catalyzed Intermolecular Oxidative Sulfamidation of Aldehydes: A Mild Efficient Synthesis of *N*-Sulfonylcarboxamides

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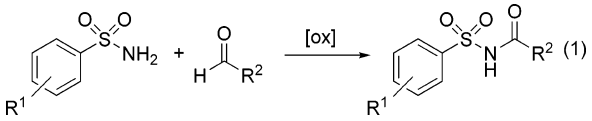
The development of mild oxidative C−H functionalization reactions remains a significant challenge in organic chemistry. In particular, major efforts in recent years on the utilization of nitrenes for C−H activation have led to considerable improvements in these protocols.[1] Accordingly, these advancements have resulted in application of such technology in the context of complex molecule syntheses.[2]

Recently we initiated a program directed toward the use of nitrenes for C−H activation as a means of preparing biologically active nitrogen containing heterocycles. During the course of that work, we were pleased to discover that aldehydes and sulfonamides react under rhodium(II) catalysis in the presence of an oxidant to afford *N*-sulfonylcarboxamides.[3,4] In this Communication, we report the scope and limitations of this methodology as well as preliminary mechanistic studies on this new transformation (eq 1).

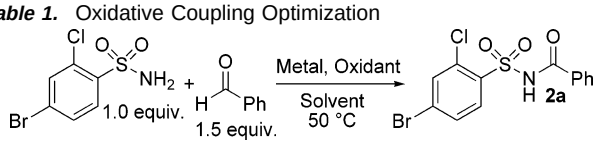


We began our investigations by examining various rhodium(II) salts in the presence of a sulfonamide, a hypervalent iodine oxidant and an aldehyde (Table 1). Exceptional to all conditions screened was the performance of $Rh_2(esp)_2$[5] which catalyzed the oxidative coupling in benzene in 29% yield (Table 1, entry 3). Examination of different solvents revealed that IPAC (isopropyl acetate) was the best medium for this reaction. Investigation of starting material stoichiometries revealed that a slight excess of aldehyde (1.2−1.5 equiv) was necessary to drive the sulfonamide to full conversion.[6] Higher yields were obtained when $PhI(OC(O)tBu)_2$ was used as the oxidant. Overall, under our optimized conditions, desired product **2a** was obtained in near quantitative yield.

A variety of sulfonamides were found to react with aromatic and aliphatic aldehydes to afford coupling products in good to excellent yields (Table 2). Remarkable functional group tolerability was observed with coupling occurring in the presence of nitro, aryl halides, trifluoromethyl, activated olefins, enolizable protons, and *N*-containing heterocycles. Interestingly, no products arising from primary benzylic C−H insertion or aziridination were observed (Table 2, entries 3, 9, and 10). Electron-poor sulfonamides make the most efficient coupling partners, whereas more electron-rich sulfonamides must be coupled at lower temperatures to attenuate decomposition.[7]

This transformation may be envisioned to proceed through several plausible mechanisms as summarized in Scheme 1. To differentiate between these pathways, we utilized several mechanistic probes. First, a primary isotope effect ($k_H/k_D = 2.5$) was observed when sulfonamide (**1a**) was reacted with an equimolar mixture of benzaldehyde and d^6-benzaldehyde indicating that C−H bond cleavage was occurring at the rate-determining step.

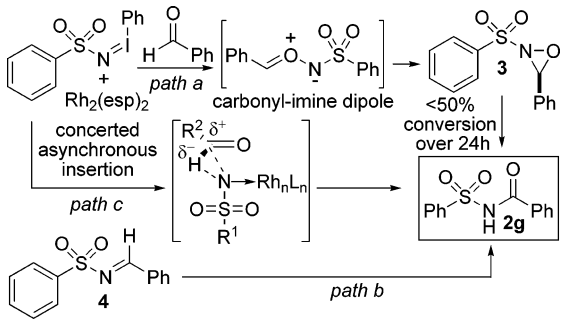
Table 1. Oxidative Coupling Optimization



entry	metal[a]	oxidant	solvent	yield[b]
1	None	$PhI(OC(O)tBu)_2$	IPAC	0
2[c]	$Rh_2(OAc)_4$	$PhI(OAc)_2$	IPAC	14
3[c]	$Rh_2(esp)_2$	$PhI(OC(O)tBu)_2$	benzene	29
4	$Rh_2(esp)_2$	$PhI(OC(O)tBu)_2$	dichloroethane	79
5[d]	$Rh_2(esp)_2$	$PhI(OC(O)tBu)_2$	IPAC	99
6	$Rh_2(oct)_4$	$PhI(OC(O)tBu)_2$	IPAC	61
7	$Rh_2(tfa)_4$	$PhI(OC(O)tBu)_2$	IPAC	3
8	$Rh_2(dosp)_2$	$PhI(OC(O)tBu)_2$	IPAC	13

[a] $Rh_2(esp)_2 = Rh_2(\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionate). [b] HPLC assay yield based on purified standard. [c] Reaction run using 1.0 equiv benzaldehyde vs 1.2 equiv sulfonamide. [d] Reaction conducted at 23 and 50 °C.

Scheme 1. Plausible Mechanisms of Rhodium-Catalyzed Coupling



To examine the viability of an oxaziridine intermediate presumably formed via the carbonyl−imine dipole (path a), compound **3** was independently synthesized[8] and subjected to the optimized reaction conditions. While the desired product was formed under these conditions, the rate of conversion was dramatically slower than the observed rates for the direct oxidative coupling. Less than 50% of the desired *N*-sulfonylcarboxamide was formed over 24 h as opposed to full conversion in 1 h at 0 °C in the oxidative sulfamidation reaction. In addition, oxaziridine **3**, which may be expected to accumulate in the reaction, *was not detected* by in-situ NMR monitoring (vide infra).

To test a pathway that would involve the intermediacy of a sulfonylaldimine (path b), sulfonylaldimine **4** containing 20% benzaldehyde was subjected to the reaction conditions. However, conversion to either oxaziridine **3** or *N*-sulfonylcarboxamide **2g**[9] was not observed suggesting that sulfonylaldimine **4** is also unlikely to be on the reaction pathway.

The coupling between benzene sulfonamide (**1d**) and ^{13}C (carbonyl) benzaldehyde was monitored by ^{13}C NMR. No ac-

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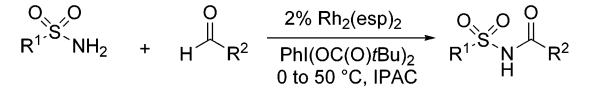
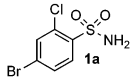
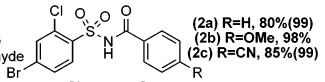
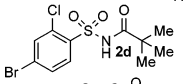
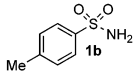
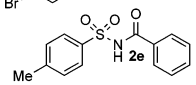
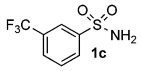
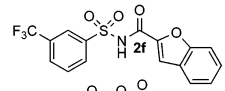
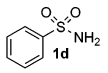
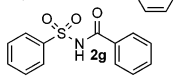
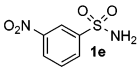
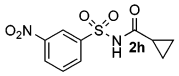
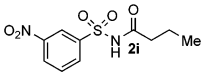
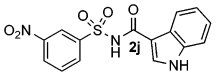
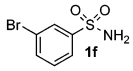
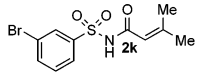
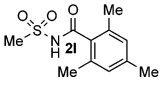
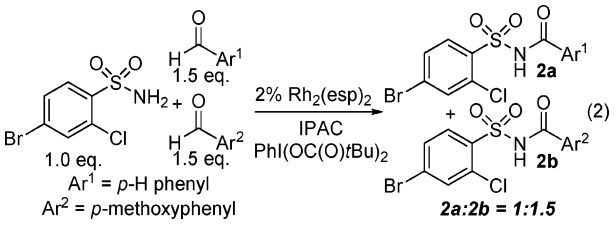
Table 2. Investigation of Oxidative Coupling Scope



Entry	Sulfonamide	Aldehyde	Product	Yield[a]
1	 **1a**	benzaldehyde *p*-anisaldehyde 4-cyanobenzaldehyde		(2a) R=H, 80%(99) (2b) R=OMe, 98% (2c) R=CN, 85%(99)
2	**1a**	*t*-BuCHO	 **2d**	67%
3[b]	 **1b**	benzaldehyde	 **2e**	90%
4	 **1c**	2-benzofuran-carboxaldehyde	 **2f**	72%
5[b]	 **1d**	benzaldehyde	 **2g**	94%
6	 **1e**	cyclopropyl carboxaldehyde	 **2h**	62%
7	**1e**	butanal	 **2i**	85%
8	**1e**	3-indole-carboxaldehyde	 **2j**	72%
9	 **1f**	3-methyl-crotonaldehyde	 **2k**	63%
10[b]	 **1g**	mesitylaldehyde	 **2l**	90%

[a] HPLC assay yield denoted in parentheses. [b] Reaction conducted at 0 °C.

cumulation of observable intermediates was detected during the course of reaction. Given that the rate determining step is C−H bond cleavage, these data suggest that the C−H bond breaking and C−N bond formation may proceed through a concerted process (path c). To probe the electronic nature of the reaction, a competitive rate experiment comparing *p*-anisaldehyde and benzaldehyde was performed in analogy with the reported correlations of both C−H amidation and aziridination chemistry (eq 2).[10] We found a slight increase in relative rate with *p*-anisaldehyde (1.5:1)[11] suggesting that the insertion itself is likely asynchronous in nature where positive charge is accumulated on the carbonyl in the transition state.[12]



It is plausible that during the process of oxidative C−H aldehydic insertion, the nitrene could be acting as either a one- or two-electron oxidant. To discern between a resonance stabilized cationic charge in the transition state versus a C−H abstraction/radical rebound pathway, phenyl acetaldehyde was employed in the reaction as an acyl radical clock.[13] The desired product from oxidative sulfamidation was isolated in 75% yield without any signs of decarbonylation.[14] This observation supports a nonradical-based mechanism within the k_d value of phenylacetaldehyde and is consistent with similar radical clock experiments conducted in C−H amidation chemistry.[15]

In summary, we have developed a general synthesis of *N*-sulfonylcarboxamides from the oxidative coupling of sulfonamides and aldehydes. An array of functional groups are tolerated under the mild conditions with respect to both sulfonamide and aldehyde. Investigations into the mechanism did not provide any evidence for the intermediacy of an oxaziridine or sulfonylaldimine. Current mechanistic data, including kinetic isotope effects and relative kinetics are consistent with a reaction that proceeds through a concerted asynchronous nitrene insertion into an aldehydic hydrogen. Applying this method to the synthesis of interesting medicinal agents as well as providing additional mechanistic insight is the subject of ongoing investigations.

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Supporting Information Available: Experimental procedures and data; tabulated NMR data and spectra of *N*-sulfonylcarboxamides (**2a**−**l**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Competition of *p*-anisaldehyde and benzaldehyde in the amidation of ethyl benzene afforded a 5:1 increase in relative rate.

(12) In the process of obtaining a direct Hammett correlation, we found no significant rate changes with *p*-Cl, *p*-^{t}Bu, or *p*-CN. (see Supporting Information.)

(13) Decarbonylation of phenylacetyl radical has been measured at $k_d = 5.2 \times 10^7$ s^{-1} at 25 °C which is within the order of magnitude of other radical clock substrates such as ethylcyclopropane ($k_d = 2 \times 10^7$ s^{-1} (ref 10b)). See also: Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

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