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Copper(II) Acetate-Induced Oxidation of Hydrazones to Diazo Compounds under Flow Conditions Followed by Dirhodium-Catalyzed Enantioselective Cyclopropanation Reactions

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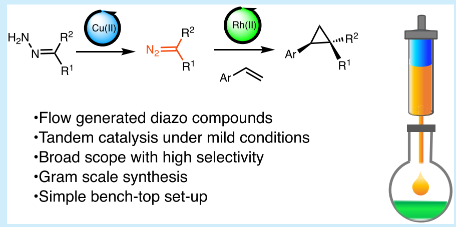
ABSTRACT: A tandem system comprising in-line diazo compound synthesis and downstream consumption in a rhodium-catalyzed cyclopropanation reaction has been developed. Passing hydrazone through a silica column absorbed with $Cu(OAc)_2$-H_2O/*N*,*N*-dimethylaminopyridine oxidized the hydrazone to generate an aryldiazoacetate in flow. The crude aryldiazoacetate elutes from this column directly into a downstream cyclopropanation reaction, catalyzed by the chiral dirhodium tetracarboxylates, Rh_2(*R*-*p*-Ph-TPCP)$_4$ and Rh_2(*R*-PTAD)$_4$. This convenient flow to batch method was applied to the synthesis of a range of 1,2-diarylcyclopropane-1-carboxylates in high yields and with high levels of enantioselectivity.



Diazo compounds are versatile reagents, capable of initiating a wide variety of synthetically useful reactions.[1−4] Particularly useful are their metal-catalyzed reactions to generate metal carbene intermediates that can be used in many enantioselective reactions such as cyclopropanation,[5−7] cyclopropenation,[3,8,9] C−H functionalization,[10−13] and ylide rearrangements.[14−16] Aryldiazoacetates have generated considerable interest in recent years because they can form donor/acceptor metal carbenes, an important class of reactive carbenes with attenuated reactivity due to the presence of the aryl group acting as a donor group.[12,17] The high energy associated with diazo compounds is helpful for the generation of the highly reactive metal carbene intermediates, but this also raises concerns regarding safety issues in handling the diazo compounds.[18] Consequently, a vast majority of studies related to diazo compounds have been relatively small-scale reactions conducted in the academic arena, although a few highly significant large-scale processes have been reported.[19−24]

In recent years, the development of continuous-flow techniques for the synthesis and immediate consumption of diazo compounds has generated considerable interest because it opens up the potential of running large-scale reactions without having large amounts of diazo compound present at any one time.[25−29] Traditional methods of diazo synthesis applied in the flow procedures use stoichiometric and/or expensive reagents and often need additional in-line purification processes to remove byproducts that would interfere in the subsequent carbene reaction.[19,23,27,30−34] To overcome these challenges, we have been exploring mild catalytic methods to oxidize hydrazones with the eventual goal of developing a practical method for generating aryldiazoacetates. During these studies, we discovered that copper acetate in the presence of DMAP is a very fast and effective catalytic system for the oxidation of hydrazones under very mild conditions using air as the terminal oxidant.[35] Having established the batch reaction, we are now developing flow methods for the synthesis of the aryldiazoacetates. We are interested in two distinct applications, a process potentially amenable for industrial scale[36] and a technically simpler lab-top procedure.

In the lab-based procedure described herein, the key requirements are to have a reliable method for the oxidation of the hydrazone and for the resulting aryldiazoacetate to be directly introduced into the rhodium-catalyzed reaction without isolation. Unlike the industrial-scale application, the cost of the $Cu(OAc)_2{\cdot}H_2O$ is not a major factor. Indeed, it is more important to have a procedurally simple method, ensuring complete consumption of the hydrazone, because any residual hydrazone could potentially poison the rhodium-catalyzed reaction. Therefore, these studies were conducted with an excess of copper salt in a column to avoid the technical challenges of requiring regeneration of copper(II) using oxygen as the terminal oxidant and to ensure complete hydrazone consumption.

The first stage of the study was to determine suitable flow conditions for full conversion of hydrazones to diazo compounds with a short residence time (τ) for achieving high efficiency and avoiding further side reactions. As shown in

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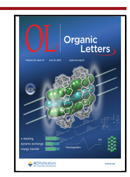
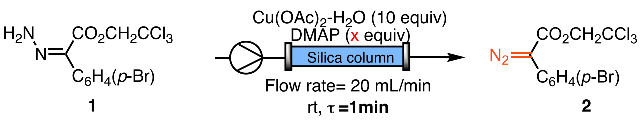


Table 1, to minimize the eluted DMAP's hazardous effect in the downstream carbene reaction, 5 equiv of DMAP mixed

Table 1. Optimization of Aryldiazoacetate Formation in Flow



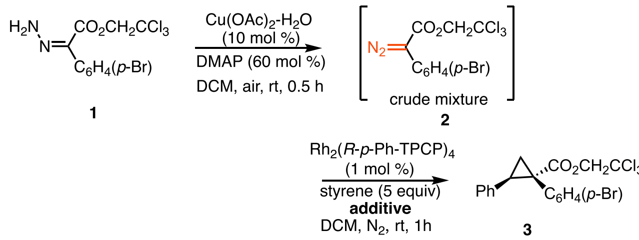
entry	eluent	DMAP (equiv)	isolated yield of **2** (%) first[a]	second[a]	third[a]
1	DCM	5	30	22	24[b]
2	DMAP/DCM[c]	5	44	35	39[b]
3	DMAP/DCM[c]	10	96	88	82

[a]The column was recycled three times. [b]The column was flushed with air for 10 min before the third batch of hydrazone was loaded. [c]The eluent concentration is 0.06 mol/L DMAP in DCM.

with 10 equiv of $Cu(OAc)_2{\cdot}H_2O$ and 4 g silica were initially packed in the column (Table 1, entries 1 and 2). However, the hydrazone was not fully converted, although flushing the column with air before the third run and including DMAP in the eluent (0.06 M) did increase the conversion. We hypothesized that without enough base to entirely activate the $Cu(OAc)_2{\cdot}H_2O$ catalyst to accelerate the oxidation reaction,[35] the column efficiency was insufficient given the limited residence time (1 min). We therefore packed 10 equiv of DMAP with $Cu(OAc)_2{\cdot}H_2O$ in the column and used DMAP/DCM as the eluent to keep the $Cu(OAc)_2{\cdot}H_2O$ saturated with base coordination. The new conditions (Table 1, entry 3) gave full hydrazone conversion for three sequential batches. Hydrazone **1** (0.2 mmol) was added on the top of the column, and aryldiazoacetate **2** was obtained at the bottom of the column in 1 min at room temperature. From the crude ^1H NMR, the reaction was shown to be very clean with only a trace amount of azine dimer formed. This high column efficiency was maintained for three batches with no requirement of air flushing or catalyst recharging.

The next step was to combine the upstream hydrazone oxidation with the downstream cyclopropanation reaction to determine the compatibility of the two reactions. This was initially explored as a batch-to-batch procedure, and the key results are summarized in Table 2. Hydrazone oxidation was conducted in a vial under catalytic conditions of $Cu(OAc)_2{\cdot}H_2O$ (10 mol %) and DMAP (60 mol %) in dichloromethane (DCM). The oxidation reaction mixture was stirred open to air, and once the reaction had reached completion, the formed crude aryldiazoacetate **2** was directly injected into a second vial with styrene, $Rh_2(R\text{-}p\text{-}Ph\text{-}TPCP)_4$, and 4 Å molecular sieves (MS) in dichloromethane under N_2 for the tandem cyclopropanation reaction. Under these conditions, the cyclopropane **3** was formed in only 18% yield and the level of enantioselectivity was moderate (77% ee). Most of the aryldiazoacetate **2** remained unreacted (Table 2, entry 1), presumably because the DMAP required for the hydrazone oxidation suppresses the reactivity of the Rh(II) catalyst in the second step. We have recently shown that HFIP as an additive in rhodium-catalyzed reactions can limit interference by nucleophilic heterocycles.[37] Indeed, this was also the case here, as repeating the reaction with 20 equiv of HFIP generated the cyclopropane **3** in 64% yield with 97% ee (Table 2, entry 2). Insertion of O−H into water was a side product,

Table 2. Optimization of the Sequential Reactions under Batch Conditions



entry	condition variation	additive	yield (%)	ee (%)
1	–	4 Å MS	18	77
2	–	HFIP	64	97
3	silica[a]	HFIP	67	98
4	silica[b]	HFIP	72	97

[a]The first reaction vial was charged with 40 mg of silica powder. [b]The solution of **2** was added to the cyclopropanation reactor at a rate of 0.05 mL/min. See the Supporting Information for the detailed procedure.

but this could be eliminated by adding silica to the copper acetate in the first oxidation step (Table 2, entry 3). Further enhancement of the yield of **3** (72%) was achieved by adding the crude aryldiazoacetate **2** dropwise to the rhodium-catalyzed reaction. These results indicate that a copper acetate-impregnated silica column should be a useful solid phase for generating aryldiazoacetates and would likely trap water from passing through the rhodium-catalyzed reaction.

ReactIR studies were conducted to understand further the role of DMAP and HFIP in the rhodium-catalyzed reaction (Figure 1). When the $Rh_2(R\text{-}p\text{-}Ph\text{-}TPCP)_4$ catalyst (1 mol %

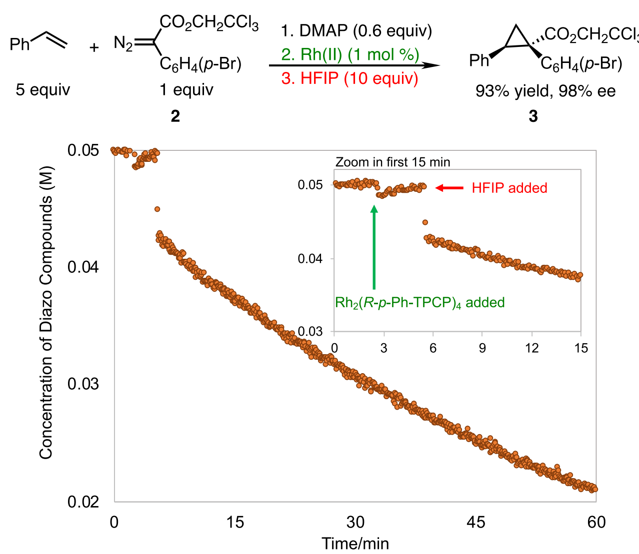


Figure 1. Kinetic investigation of the effect of DMAP and HFIP on Rh(II)-catalyzed cyclopropanation.

in 0.1 mL of dichloromethane) was injected into a solution of the aryldiazoacetate **2**, styrene, and DMAP in dichloromethane, the distinctive IR signal for the diazo compound did not change. However, when HFIP (10 equiv) was injected, the reaction was initiated and proceeded to completion, generating the cyclopropane **3** in 93% yield and 98% ee (note the apparent rapid decrease in the level of aryldiazoacetate **2** upon addition of HFIP is due to a change in the concentration

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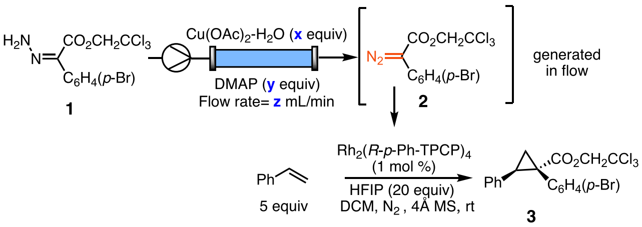
of **2** and not due to an initial fast reaction). The overall kinetic profile suggested that DMAP leads to catalyst deactivation, likely by coordinating to the Rh(II) catalyst.[38,39] HFIP is proposed either to protonate the DMAP or to act as a hydrogen bond donor to interact with DMAP and suppress its deleterious coordination influence on the Rh(II)-catalyzed carbene reaction. A ^{1}H NMR study also showed that the HFIP and diazo compounds **2** influenced each other's peak shifts (see the Supporting Information), which suggests that the reaction may also be affected by the hydrogen bonding between the diazo compound and HFIP.[40,41] These studies indicate that DMAP that might leach through the column under the flow conditions can be neutralized by HFIP present in the rhodium-catalyzed reaction flask.

Having established the key requirements of the hydrazone oxidation and the cyclopropanation reactions, a flow system was set up using a column consisting of a top layer of $Cu(OAc)_2 \cdot H_2O$ and DMAP mixed with silica and a lower layer of silica to retain much of the DMAP and the water formed. The hydrazone is added at the top of the column, and the aryldiazoacetate eluent is directly added to the downstream flask to perform the rhodium-catalyzed carbene reaction. The flow rate of this room temperature column is controlled by a syringe pump, and a nitrogen balloon on the flask provides the inert atmosphere for carbene reactions and balances the pressure during the reaction process. To maximize the overall efficiency, the semibatch downstream process was optimized as shown in Table 3. We first applied excess Cu/DMAP [10 equiv of $Cu(OAc)_2 \cdot H_2O$ and 22 equiv of DMAP] and a fast flow rate to ensure full hydrazone conversion while minimizing the residence time to avoid side reaction of aryldiazoacetate **2** and excess eluent injection into the downstream reaction flask (Table 3, entries 1 and 2). Although the column fully converted the hydrazone **1** to the aryldiazoacetate **2** according to ^{1}H NMR, the reactivity and selectivity in the cyclopropanation step were poor, presumably because an overwhelming amount of DMAP had eluted from the upstream column. Therefore, the flow rate and the equivalents of DMAP and eluent were screened to achieve high efficiency in both the upstream hydrazone oxidation and the downstream cyclopropanation. As shown in entry 7 of Table 3, the condition with 10 equiv of $Cu(OAc)_2 \cdot H_2O$ and DMAP, a 1 mL/min flow rate, and DMAP/DCM as the eluent in the column generated the aryldiazoacetate **2** effectively and delivered the cyclopropane **3** in 75% yield with 97% ee. These results indicate that DMAP and the water byproduct are effectively absorbed by the silica or deactivated by the HFIP or the 4 Å MS present in the rhodium-catalyzed reaction mixture.

With an optimized flow procedure in hand, we explored the reaction scope of diazo compound generation in flow followed by direct introduction into the rhodium-catalyzed reactions. The reactions were conducted with various aryldiazoacetates and styrene derivatives, and the results are summarized in Figure 2. In the case of relatively uncrowded styrene derivatives, $Rh_2(R\text{-}p\text{-}Ph\text{-}TPCP)_4$ is an effective catalyst, as illustrated by the formation of cyclopropanes **4**−**12** in 70−78% yields with high levels of enantioselectivity (91−97% ee). In contrast, $Rh_2(R\text{-}p\text{-}Ph\text{-}TPCP)_4$ was less effective in reactions with more bulky styrene derivatives or 1,1-diphenylethylene, and the formation of cyclopropanes **13**−**15** was best achieved using $Rh_2(R\text{-}PTAD)_4$ as the catalyst (56−61% yield and 67−94% ee). Comparison studies were conducted in which the aryldiazoacetate was prepared in a catalytic batch reaction

Table 3. Optimization of Flow Batch Reaction Conditions



entry	x	y	z	eluent	yield (%)	ee (%)
1	10	22	20	DCM	52	43
2	10	22	5	DCM	79	55
3	10	10	2	DCM	73	93
4	10	5	2	DCM	31	96
5	10	5	2	DMAP/DCM	43	90
6	10	10	2	DMAP/DCM	76	92
7	10	10	1	DMAP/DCM	**75**	**97**
8	10	5	0.5	DMAP/DCM	30	95
9	5	10	1	DMAP/DCM	73	97
10	2.5	10	1	DMAP/DCM	46	96
11[a]	10	10	1	DMAP/DCM	21	90
12[b]	10	10	1	DMAP/DCM	31	96

[a]Cyclopropanation was performed with 0.1 mol % $Rh_2(R\text{-}p\text{-}Ph\text{-}TPCP)_4$. [b]Cyclopropanation was performed with 5 equiv of HFIP.

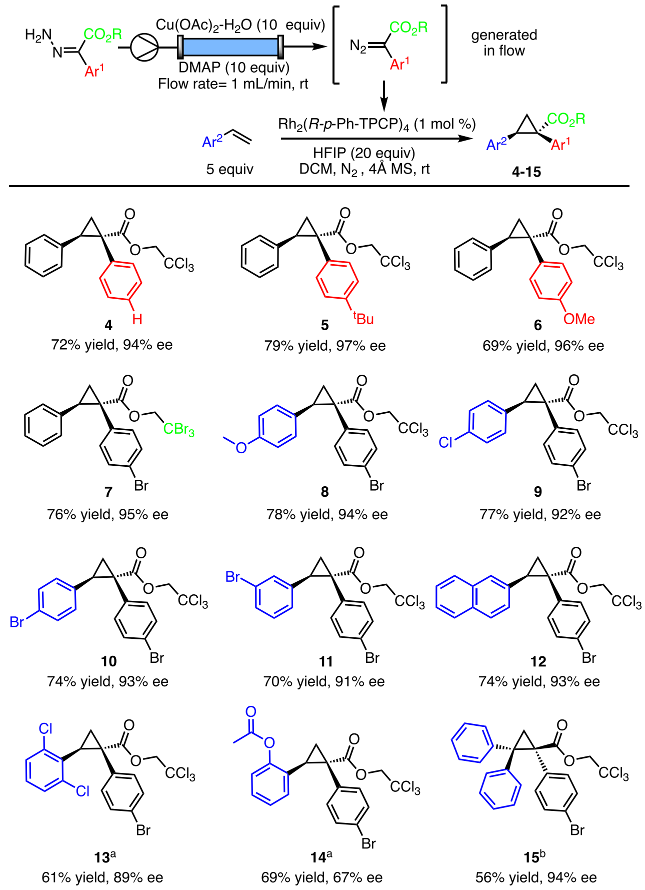


Figure 2. Synthesis of tandem diazo compounds and the cyclopropanation scope. [a]Reaction with $Rh_2(R\text{-}PTAD)_4$ at 40 °C. [b]Reaction with $Rh_2(R\text{-}PTAD)_4$ at rt.

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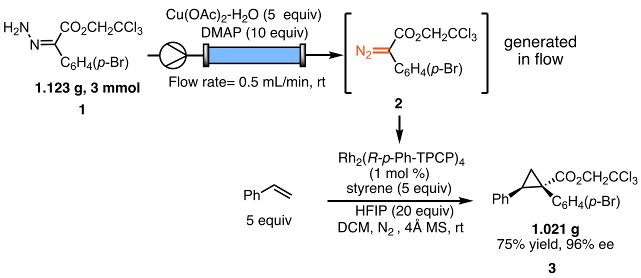
[with 10 mol % $Cu(OAc)_2 \cdot H_2O$ (same conditions as in entry 4 of Table 2)] followed by addition of the aryldiazoacetate to the rhodium-catalyzed reaction mixtures, and the results were very similar to those of the flow batch reactions described in Figure 2 (see the Supporting Information for complete details).

On the basis of the results presented above, we further investigated the practicality of this continuous-flow procedure by conducting a gram-scale reaction with only 5 equiv of $Cu(OAc)_2 \cdot H_2O$ mixed with 10 equiv of DMAP in the column to convert a hydrazone to its diazo compound and subsequently injected it into the downstream cyclopropanation reaction mixture. As shown in Scheme 1, with 3 mmol of hydrazone **2** (1.123 g) as starting material, the final 1.021 g of cyclopropanation product **3** was obtained with 75% yield and 96% ee (see the Supporting Information for the detailed procedure). The result herein demonstrates the practicality of this procedure for accessing diazo compounds and their related cyclopropanation products in useful quantities effectively and safely. Control experiments were also conducted to show that the copper acetate catalyst could be reused at least twice and then regenerated by flushing with air, and a separate cartridge of silica could be used for easy replacement (see the Supporting Information for details).

Scheme 1. Gram-Scale Synthesis with a Bench-Top Flow Procedure



In conclusion, a convenient bench-top flow procedure for generating a diazo compound through Cu(II)-induced hydrazone oxidation in a simple setup using a Cu(II)/DMAP mixed silica column is presented. The resulting solution of the diazo compound can be directly added to the rhodium-catalyzed cyclopropanation reaction mixture without further purification. HFIP played a crucial role in protecting the rhodium-catalyzed reaction from interference from reagents used in the first step. The advantage of this approach is the ease of the process and the enhanced safety considerations in generating the diazo compound in flow. It requires introduction of the hydrazone at the top of the column without the need to concentrate or isolate the formed diazo compound before the subsequent carbene reaction. The process avoids the engineering challenges of regeneration of the copper(II) salt using air as the terminal oxidant, although a process using copper in catalytic amounts may be required for a practical industrial-scale process.[36]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01580.

Experimental data for the synthesis and characterization of the compounds generated and for the kinetic studies (PDF)

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Notes

The authors declare the following competing financial interest(s): H.M.L.D. is a named inventor on a patent entitled "Dirhodium Catalyst Compositions and Synthetic Processes Related Thereto" (U.S. 8,974,428, issued March 10, 2015).

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