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

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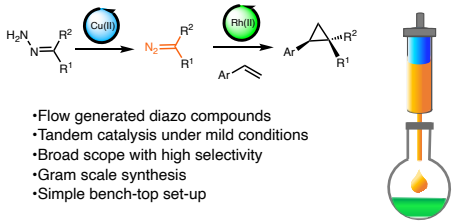
Supporting Information Placeholder



ABSTRACT: A tandem system comprising of 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 (DMAP) 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)$_4$ or 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, the 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]

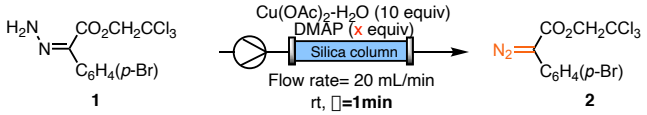
In recent years, the development of continuous-flow techniques for the synthesis and immediate consumption of diazo compounds has generated considerable interest because it opens up the potential of running large scale reactions without having large amounts of diazo compound present at any one time.[25-29] 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 by-products that would interfere in the subsequent carbene reaction.[19, 23, 27, 30-34] In order 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 $Cu(OAc)_2$-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 Table 1, to minimize the eluted DMAP's hazardous effect in the downstream carbene reaction, 5 equiv of DMAP mixed with 10 equiv of $Cu(OAc)_2$-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 3rd run and including DMAP in the eluent (0.06 M) did increase the conversion. We hypothesized that without enough base to entirely activate the $Cu(OAc)_2$-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 $Cu(OAc)_2$-H_2O in the column and used DMAP/DCM as the eluent to keep the $Cu(OAc)_2$-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 column and aryldiazoacetate **2** was obtained at the bottom of the column in 1 min at room temperature. From the crude ^{1}H 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 3 batches with no requirement of air flushing or catalyst recharging.

Table 1. Optimization of aryldiazoacetate formation in flow

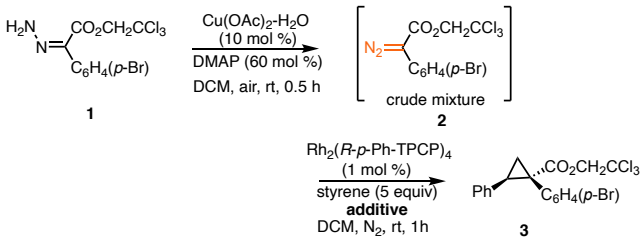


entry	eluent	DMAP (equiv)	isolated yield of **2** (%)		
			1st*	2nd*	3rd*
1	DCM	5	30	22	24[a]
2	DMAP/DCM[b]	5	44	35	39[a]
3	DMAP/DCM[b]	10	96	88	82

*The column was recycled 3 times. [a]The column was flushed with air for 10 min before loading the 3rd batch of hydrazone. [b]Eluent concentration is 0.06 mol/L DMAP in DCM.

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. The hydrazone oxidation was conducted in a vial under catalytic conditions of $Cu(OAc)_2$-H_2O (10 mol %) and DMAP (60 mol %) in dichloromethane (DCM). The oxidation reaction mixture was stirred open to air and once completed, the formed crude aryldiazoacetate **2** was directly injected to a second vial with styrene, Rh_2(*R*-*p*-Ph-TPCP)$_4$, and 4Å 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), O-H Insertion into water was a side product but this could be eliminated if silica was added 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 though the rhodium-catalyzed reaction.

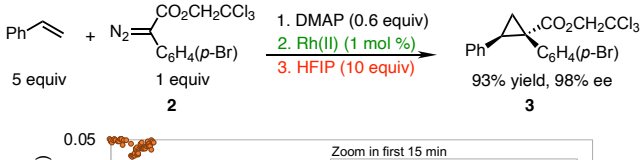
Table 2. Optimization of the sequential reactions under batch conditions



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

[a] 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 SI for the detailed procedure.

ReactIR studies were conducted to understand further the role of DMAP and HFIP in the rhodium-catalyzed reaction (Figure 1). When Rh_2(*R*-*p*-Ph-TPCP)$_4$ catalyst (1 mol % in 0.1 mL dichloromethane) was injected to 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 initiated and went to completion, generating the cyclopropane **3** in 93% yield and 98% ee (note the apparent rapid decrease in aryldiazoacetate **2** on addition of HFIP is due to a change in the concentration 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 to either 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 SI), 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.



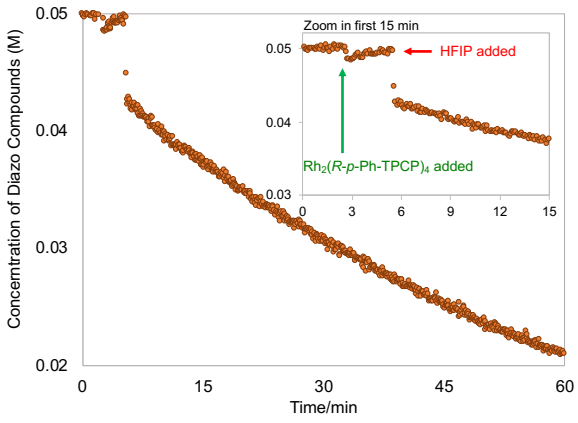
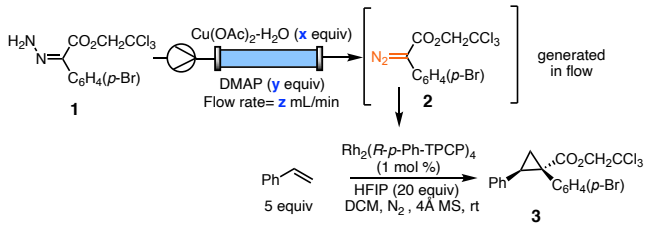


Figure 1. Kinetic investigation of the effect of DMAP and HFIP on Rh(II) catalyzed cyclopropanation

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 $Cu(OAc)_2$-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 semi-batch downstream process was optimized as shown in Table 3. We first applied excess Cu/DMAP (10 equiv $Cu(OAc)_2$-H_2O, 22 equiv 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, 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 of an overwhelming amount of DMAP had eluted from the upstream column. Therefore, the flow rate, equiv of DMAP and eluent were screened in order to achieve high efficiency in both the upstream hydrazone oxidation and the downstream cyclopropanation. As shown in Table 3, entry 7 (the condition with 10 equiv of $Cu(OAc)_2$-H_2O and DMAP, 1 mL/min flow rate, and DMAP/DCM as eluent in the column) generated the aryldiazoacetate **2** effectively and delivered the cyclopropane **3** in 75% yield with 97% ee. The decent yield suggested that most of the DMAP and the formed side-product, water, were effectively trapped by the silica column as well as the 4Å MS, and that HFIP in the cyclopropanation flask helped to minimize the deleterious effects of DMAP.

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*-*p*-Ph-TPCP)$_4$. [b]. Cyclopropanation was performed with 5 equiv HFIP.

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*-*p*-Ph-TPCP)$_4$ is an effective catalyst, as illustrated by the formation of the cyclopropanes **4-12** in 70-78% yield and with high levels of enantioselectivity (91-97% ee). In contrast, Rh_2(*R*-*p*-Ph-TPCP)$_4$ was less effective in reactions with more bulky styrene derivatives or 1,1-diphenylethylene, and the formation of the cyclopropanes **13-15** was best achieved using Rh_2(*R*-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 (with 10 mol % $Cu(OAc)_2$-H_2O, conditions the same as Table 2, entry 4) followed by addition of the aryldiazoacetate to the rhodium catalyzed reactions and the results were very similar to the flow-batch reactions described in Figure 2 (see SI for complete details).

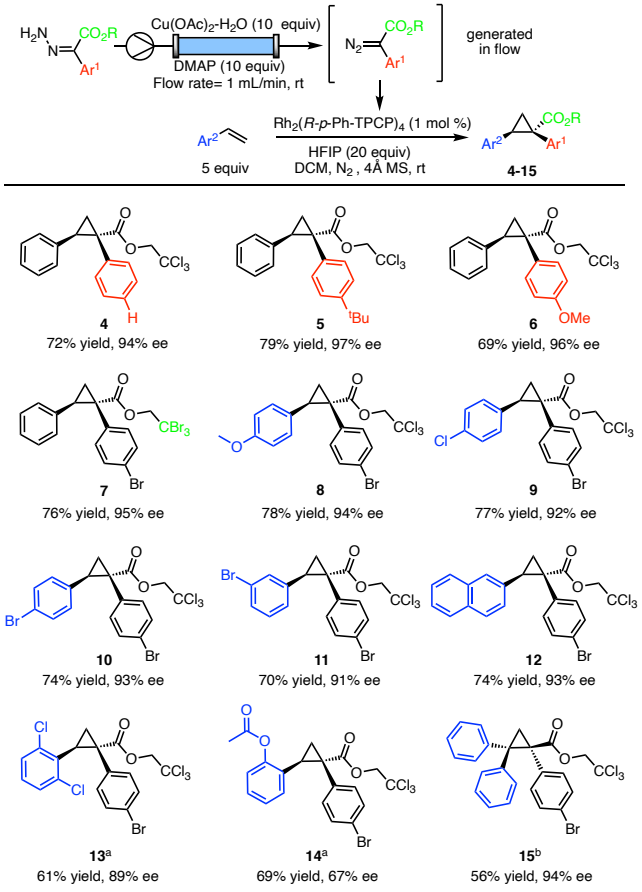
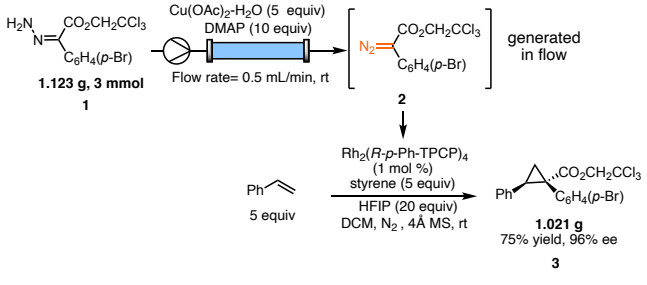


Figure 2. Tandem diazo compounds synthesis and the cyclopropanation scope. [a]Reaction with Rh_2(*R*-PTAD)$_4$ at 40 °C. [b]Reaction with Rh_2(*R*-PTAD)$_4$ at rt.

Based on the results above, we further investigated the practicality of this continuous-flow procedure by conducting a gram-scale reaction with only 5 equiv of $Cu(OAc)_2$-H_2O mixed with 10 equivalents DMAP in the column to convert a hydrazone to its diazo compound and subsequently injected it to the downstream cyclopropanation reaction. As shown in Scheme 1,

with 3 mmol hydrazone **2** (1.123 g) as starting material, the final 1.021g of cyclopropanation product **3** was obtained with 75% yield and 96% ee (see SI for detailed procedure). The result herein demonstrates the practicality of this procedure to access 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, then be regenerated by flushing with air, and a separate cartridge of silica could be used for easy replacement (see SI for details).

Scheme 1. Gram scale synthesis with bench-top flow procedure



In conclusion, a convenient bench-top flow procedure to generate diazo compound through Cu(II)-induced hydrazone oxidation in a simple set up using a Cu(II)-DMAP mixed silica column. The resulting solution of the diazo compound can be directly added to the rhodium-catalyzed cyclopropanation reaction 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 on the ACS Publications website.

Experimental data for the synthesis and characterization of the compounds generated and for the kinetic studies.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

HMLD is a named inventor on a patent entitled, Dirhodium Catalyst Compositions and Synthetic Processes Related Thereto (US 8,974,428, issued March 10, 2015).

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REFERENCES

(1) Mix, K. A.; Aronoff, M. R.; Raines, R. T. Diazo Compounds: Versatile Tools for Chemical Biology. *ACS Chem. Biol.* **2016,** *11*, 3233-3244.

(2) Ciszewski, L. W.; Rybicka-Jasinska, K.; Gryko, D. Recent Developments in Photochemical Reactions of Diazo Compounds. *Org. Biomol. Chem.* **2019,** *17*, 432-448.

(3) Deng, Y.; Jing, C.; Doyle, M. P. Dinitrogen Extrusion from Enoldiazo Compounds Under Thermal Conditions: Synthesis of Donor-Acceptor Cyclopropenes. *Chem. Commun.* **2015,** *51*, 12924-12927.

(4) Li, P.; Zhao, J.; Shi, L.; Wang, J.; Shi, X.; Li, F. Iodine-Catalyzed Diazo Activation to Access Radical Reactivity. *Nat. Commun.* **2018,** *9*, 1972.

(5) Damiano, C.; Sonzini, P.; Gallo, E. Iron catalysts with N-ligands for carbene transfer of diazo reagents. *Chem. Soc. Rev.* **2020,** *49*, 4867-4905.

(6) Nam, D.; Steck, V.; Potenzino, R. J.; Fasan, R. A Diverse Library of Chiral Cyclopropane Scaffolds via Chemoenzymatic Assembly and Diversification of Cyclopropyl Ketones. *J. Am. Chem. Soc.* **2021,** *143*, 2221-2231.

(7)Wei, B.; Sharland, J. C.; Lin, P.; Wilkerson-Hill, S. M.; Fullilove, F. A.; McKinnon, S.; Blackmond, D. G.; Davies, H. M. L. In Situ Kinetic Studies of Rh(II)-Catalyzed Asymmetric Cyclopropanation with Low Catalyst Loadings. *ACS Catal.* **2020,** *10*, 1161-1170.

(8) Briones, J. F.; Davies, H. M. L. Rh_2(S-PTAD)$_4$-Catalyzed Asymmetric Cyclopropenation of Aryl Alkynes. *Tetrahedron* **2011,** *67*, 4313-4317.

(9) Chen, L.; Leslie, D.; Coleman, M. G.; Mack, J. Recyclable Heterogeneous Metal Foil-Catalyzed Cyclopropenation of Alkynes and Diazoacetates Under Solvent-Free Mechanochemical Reaction Conditions. *Chem. Sci.* **2018,** *9*, 4650-4661.

(10) Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Perez, P. J. The Carbene Insertion Methodology for the Catalytic Functionalization of Unreactive Hydrocarbons: No Classical C-H Activation, but Efficient C-H Functionalization. *Dalton Trans.* **2006**, 5559-5566.

(11) Davies, H. M. L.; Hansen, T.; Churchill, M. R. Catalytic Asymmetric C-H Activation of Alkanes and Tetrahydrofuran. *J. Am. Chem. Soc.* **2000,** *122*, 3063-3070.

(12) Davies, H. M. L.; Liao, K. Dirhodium Tetracarboxylates as Catalysts for Selective Intermolecular C – H Functionalization. *Nat. Rev. Chem.* **2019,** *3*, 347-360.

(13) Bergstrom, B. D.; Nickerson, L. A.; Shaw, J. T.; Souza, L. W. Transition Metal Catalyzed Insertion Reactions with Donor/Donor Carbenes. *Angew. Chem. Int. Ed.* **2020,** *132*, 2-17.

(14) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. Highly Effective Catalytic Methods for Ylide Generation From Diazo Compounds. Mechanism of the Rhodium- and Copper-Catalyzed Reactions with Allylic Compounds. *J. Org. Chem.* **1981,** *46*, 5094-5102.

(15) Jana, S.; Guo, Y.; Koenigs, R. M. Recent Perspectives on Rearrangement Reactions of Ylides via Carbene Transfer Reactions. *Chem. Eur. J.* **2021,** *27*, 1270-1281.

(16) Jones, A. C.; May, J. A.; Sarpong, R.; Stoltz, B. M. Toward a Symphony of Reactivity: Cascades Involving Catalysis and Sigmatropic Rearrangements. *Angew. Chem. Int. Ed.* **2014,** *53*, 2556-2591.

(17) Guptill, D. M.; Davies, H. M. L. 2,2,2-Trichloroethyl Aryldiazoacetates as Robust Reagents for the Enantioselective C-H Functionalization of Methyl Ethers. *J. Am. Chem. Soc.* **2014,** *136*, 17718-17721.

(18) Green, S. P.; Wheelhouse, K. M.; Payne, A. D.; Hallett, J. P.; Miller, P. W.; Bull, J. A. Thermal Stability and Explosive Hazard Assessment of Diazo Compounds and Diazo Transfer Reagents. *Org. Process Res. Dev.* **2020,** *24*, 67-84.

(19) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. Modern Organic Synthesis with Alpha-Diazocarbonyl Compounds. *Chem. Rev.* **2015,** *115*, 9981-10080.

(20) Bajaj, P.; Sreenilayam, G.; Tyagi, V.; Fasan, R. Gram-Scale Synthesis of Chiral Cyclopropane-Containing Drugs and Drug Precursors with Engineered Myoglobin Catalysts Featuring Complementary Stereoselectivity. *Angew. Chem. Int. Ed.* **2016,** *55*, 16110-16114.

(21) Gage, J. R.; Chen, F.; Dong, C.; Gonzalez, M. A.; Jiang, Y.; Luo, Y.; McLaws, M. D.; Tao, J. Semicontinuous Process for GMP Manufacture of a Carbapenem Intermediate via Carbene Insertion Using an Immobilized Rhodium Catalyst. *Org. Process Res. Dev.* **2020,** *24*, 2025-2033.

(22) Bien, J.; Davulcu, A.; DelMonte, A. J.; Fraunhoffer, K. J.; Gao, Z.; Hang, C.; Hsiao, Y.; Hu, W.; Katipally, K.; Littke, A.; Pedro, A.; Qiu, Y.; Sandoval, M.; Schild, R.; Soltani, M.; Tedesco, A.; Vanyo, D.; Vemishetti, P.; Waltermire, R. E. The First Kilogram Synthesis of Beclabuvir, an HCV NS5B Polymerase Inhibitor. *Org. Process Res. Dev.* **2018,** *22*, 1393-1408.

(23) Sheeran, J. W.; Campbell, K.; Breen, C. P.; Hummel, G.; Huang, C.; Datta, A.; Boyer, S. H.; Hecker, S. J.; Bio, M. M.; Fang, Y.-Q.; Ford, D. D.; Russell, M. G. Scalable On-Demand Production of Purified Diazomethane Suitable for Sensitive Catalytic Reactions. *Org. Process Res. Dev.* **2020,** *25*, 522-528.

(24) Anthes, R.; Bello, O.; Benoit, S.; Chen, C. K.; Corbett, E.; Corbett, R. M.; DelMonte, A. J.; Gingras, S.; Livingston, R.; Sausker, J.; Soumeillant, M. Kilogram Synthesis of a Selective Serotonin Reuptake Inhibitor. *Org. Process Res. Dev.* **2008,** *12*, 168-177.

(25) Tran, D. N.; Battilocchio, C.; Lou, S. B.; Hawkins, J. M.; Ley, S. V. Flow Chemistry as a Discovery Tool to Access sp(2)-sp(3) Cross-Coupling Reactions via Diazo Compounds. *Chem. Sci.* **2015,** *6*, 1120-1125.

(26) Fuse, S.; Otake, Y.; Nakamura, H. Integrated Micro-Flow Synthesis Based on Photochemical Wolff Rearrangement. *Eur. J. Org. Chem.* **2017,** *2017*, 6466-6473.

(27) Muller, S. T.; Murat, A.; Maillos, D.; Lesimple, P.; Hellier, P.; Wirth, T. Rapid Generation and Safe Use of Carbenes Enabled by a Novel Flow Protocol with In-line IR spectroscopy. *Chem. Eur. J.* **2015,** *21*, 7016-7020.

(28) Poh, J. S.; Tran, D. N.; Battilocchio, C.; Hawkins, J. M.; Ley, S. V. A Versatile Room-Temperature Route to Di- and Trisubstituted Allenes Using Flow-Generated Diazo Compounds. *Angew. Chem. Int. Ed.* **2015,** *54*, 7920-7923.

(29) Rackl, D.; Yoo, C. J.; Jones, C. W.; Davies, H. M. L. Synthesis of Donor/Acceptor-Substituted Diazo Compounds in Flow and Their Application in Enantioselective Dirhodium-Catalyzed Cyclopropanation and C-H Functionalization. *Org. Lett.* **2017,** *19*, 3055-3058.

(30) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. Diazotransfer Reactions with p-Acetamidobenzenesulfonyl Azide. *Synthetic Communications* **1987,** *17*, 1709-1716.

(31) Sullivan, R. J.; Freure, G. P. R.; Newman, S. G. Overcoming Scope Limitations in Cross-Coupling of Diazo Nucleophiles by Manipulating Catalyst Speciation and Using Flow Diazo Generation. *ACS Catal.* **2019,** *9*, 5623-5630.

(32) Levesque, E.; Laporte, S. T.; Charette, A. B. Continuous Flow Synthesis and Purification of Aryldiazomethanes through Hydrazone Fragmentation. *Angew. Chem. Int. Ed.* **2017,** *56*, 837-841.

(33) Maurya, R. A.; Park, C. P.; Lee, J. H.; Kim, D. P. Continuous In Situ Generation, Separation, and Reaction of Diazomethane in a Dual-Channel Microreactor. *Angew. Chem. Int. Ed.* **2011,** *50*, 5952-5955.

(34) Mastronardi, F. G., B.; Kappe, C. O Continuous Flow Generation and Reactions of Anhydrous Diazomethane Using a Teflon AF-2400 Tube-in-Tube Reactor. *Org. Lett.* **2013,** *15*, 5590-5593.

(35) Liu, W.; Twilton, J.; Wei, B.; Lee, M.; Hopkins, M. N.; Bacsa, J.; Stahl, S. S.; Davies, H. M. L. Copper-Catalyzed Oxidation of Hydrazones to Diazo Compounds Using Oxygen as the Terminal Oxidant. *ACS Catal.* **2021,** *11*, 2676-2683.

(36) Hatridge, T. A.; Wei, B.; Davies, H. M. L.; Jones, C. W. Copper-Catalyzed, Aerobic Oxidation of Trichloroethyl Aryl Hydrazonoacetate in a Three-Phase Packed Bed Reactor. *Submitted to Org. Process Res. Dev.*

(37) Sharland, J. C.; Wei, B.; Hardee, D. J.; Hodges, T. R.; Gong, W.; Voight, E. A.; Davies, H. M. L. Role of Additives to Overcome Limitations of Intermolecular Rhodium-Catalyzed Asymmetric Cyclopropanation. *ChemRxiv. Preprint.* **2021,** https://doi.org/10.26434/chemrxiv.14479593.v1.

(38) Lindsay, V. N.; Nicolas, C.; Charette, A. B. Asymmetric Rh(II)-Catalyzed Cyclopropanation of Alkenes with Diacceptor Diazo Compounds: p-Methoxyphenyl Ketone as a General Stereoselectivity Controlling Group. *J. Am. Chem. Soc.* **2011,** *133*, 8972-8981.

(39) Trindade, A. F.; Coelho, J. A. S.; Afonso, C. A. M.; Veiros, L. F.; Gois, P. M. P. Fine Tuning of Dirhodium(II) Complexes: Exploring the Axial Modification. *ACS Catal.* **2012,** *2*, 370-383.

(40) Dumitrescu, L.; Azzouzi-Zriba, K.; Bonnet-Deplon, D.; Crousse, B. Nonmetal Catalyzed Insertion Reactions of Diazocarbonyls to Acid Derivatives in Fluorinated Alcohols. *Org. Lett.* **2011,** *13*, 692-695.

(41) Azzouzi-Zriba, K.; Bonnet-Delpon, D.; Crousse, B. Transition Metal-Catalyzed Cyclopropanation of Alkenes in Fluorinated Alcohols. *J. Fluor. Chem.* **2011,** *132*, 811-814.