Hexafluoroisopropanol for the Selective Deactivation of Poisonous Nucleophiles Enabling Catalytic Asymmetric Cyclopropanation of Complex Molecules.

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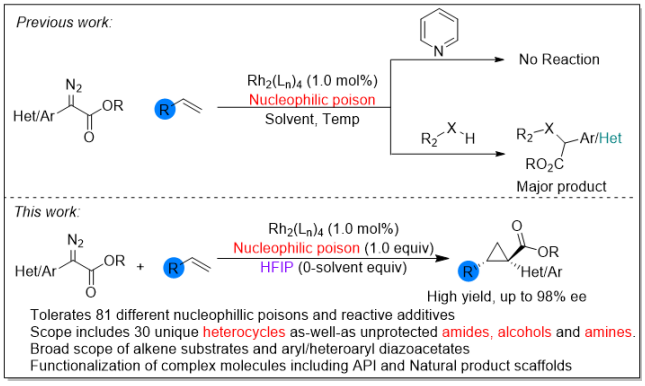
ABSTRACT: In the presence of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), nucleophilic and reactive reagents are prevented from interacting with a rhodium carbene, allowing asymmetric cyclopropanation to occur with high yield and stereoselectivity on a variety of compounds. A high-throughput screen was conducted on cyclopropanation with a complementary catalytic system in the presence of 90 different poisonous nucleophiles and varying amounts of HFIP (10 equiv - used as reaction solvent). The scope of both the aryl/heteroaryl diazoacetate and the olefin was expanded, and the study culminated in the enantioselective functionalization of complex molecules including API and natural products.

Introduction:

Asymmetric rhodium-catalyzed cyclopropanation between diazo compounds and alkenes is an important method for the synthesis of industrially relevant compounds.[1-4] When the carbene bears both a donor and an acceptor group, the cyclopropanation proceeds with high diastereoselectivity (typically >20:1 d.r.) and several chiral dirhodium catalysts have been developed to render the reaction highly enantioselective.[5,6] While the reaction can be robust and scalable, reliance on the use of a transition metal catalyst and a carbene intermediate means that the substrate scope is inherently limited. Various nucleophiles can coordinate to the rhodium center to the exclusion of the diazo compound, preventing catalytic activity (Scheme 1a).[7-10] Additionally, reactive bonds can outcompete the desired substrate and react with the carbene. Water, alcohols, and protic-amines selectively react with donor/acceptor-carbenes via the heteroatom–H bond to the exclusion of alkene traps like styrene (Scheme 1).[11,12] This significantly harms the applicability of rhodium carbene methodology to a commercial setting, where tolerance of trace impurities, along with the aza-heterocycles and reactive functionality that are common in both therapeutic compounds and natural products, is necessary. [1,2,13-15]

Previous attempts to use Rh-carbene chemistry to functionalize complex molecules containing nucleophilic sites often required the use of high catalyst loading and forcing temperatures to limit catalyst inhibition.[16] Even though several of these transformations were successful, the scope was intolerant of reactive moieties like alcohols and the observed selectivity was poor.[16,17] We have had a long-standing interest in the cyclopropanation chemistry of donor/acceptor carbenes and we wished to find a general and procedurally simple approach to conduct cyclopropanation reactions in the presence of the classic nucleophilic poisons or reactive functionality that would be considered to be incompatible with this chemistry.[18] We became intrigued with the possibility that HFIP could be an effective solution to the challenges of functional group intolerance. Reactions conducted in HFIP typically exploit its powerful hydrogen bonding ability to weaken electron rich bonds which can then react under a variety of conditions.[19-23] Other functionality like alcohols and alkenes can be engaged in a similar manner.[24-29] Most of the examples using HFIP rely on enhancing the reactivity of substrates by increasing their electrophilicity. In our case, this strong hydrogen bonding capability would be expected to deactivate nucleophilic sites that would typically poison the reaction (Scheme 1). Even though there are a few examples of the deactivating influence of HFIP,[30,31] it has not been explored extensively, particularly in the context of rhodium carbene chemistry. [7,19] HFIP, unlike other fluorinated alcohols, is



Scheme 1: Cyclopropanation in the presence of nucleophilic poisons

essentially inert to rhodium carbenes under mild conditions, and it can be easily removed by rotary evaporation, making it an attractive reaction medium.[12, 32] In this study we developed new catalytic systems with HFIP as an additive to enable high yielding and highly stereoselective cyclopropanation in the presence of a broad scope of poisonous and reactive functionality (Scheme 1b). Then, the potential of this new approach is illustrated with the stereoselective derivatization of several elaborate APIs and natural products which bear functionality that would have been previously considered incompatible with the cyclopropanation chemistry.

Results and Discussion:

We have recently become interested in exploring the role of HFIP as an additive in rhodium carbene chemistry. Very small quantities were found to enhance the enantioselectivity in rhodium catalyzed allylic C–H functionalization with 4-aryl-*N*-sulfonyl triazoles.[33] During recent studies to optimize some specific rhodium-catalyzed cyclopropanation we discovered that HFIP (10 equiv) desensitizes the reaction to water and *N,N'*-dimethylaminopyridine (DMAP).[7, 34] Given this exciting and unexpected result, we suspected that we could leverage this effect to deactivate a wide range of other nucleophilic poisons and reactive functionality that typically interfere with the cyclopropanation reaction.[19, 30, 31] HFIP can hydrogen bond with, or even formally protonate, different nucleophiles due to its relatively high acidity, preventing them from coordinating with the dirhodium catalyst and the rhodium carbene intermediate.[31] As a result, we suspected that not only could we prevent poisonous nucleophiles from inhibiting the reaction, but that we may also be able to prevent reactive species like amines and alcohols from preferentially reacting with the carbene through X–H insertion. Furthermore, HFIP is inert to the rhodium carbene as reported in previous literature studies, so the desired cyclopropanation reaction may be able to proceed even in the presence of a vast excess of HFIP.[12] In order to explore this possibility, the reaction of 1-hexene (2.5 equiv) with 2,2,2-trichloroethyl 2-(4-bromophenyl)diazo-2-acetate (**1**) catalyzed by Rh_2(*R*-TPPTTL)$_4$.[35] (**8**, 1.0 mol %) was used as a reference reaction (Table 1). The standard reaction in the absence of HFIP resulted in the formation of cyclopropane **2** in 91% yield. Five representative substrates with functionality likely to interfere with the cyclopropanation were examined. These were the tertiary amines, *N*-methyl pyrrolidine (**3**) and pyridine (**5**), and the protic substrates, *tert*-butyl alcohol (**4**) acetoacetamide (**6**) and cyclohexanone oxime (**7**). None of the cyclopropane **2** was formed when the standard reaction was conducted in the presence of 1 equiv of these poisons. When HFIP was added, however, the negative influence of these poisons could be blocked. In the presence of 10 equiv of HFIP, cyclopropanation interference no longer occurred with *N*-methyl pyrrolidine (**3**) or *tert*-butyl alcohol (**4**), whereas the use of HFIP as solvent was required to block the interference by pyridine (**5**), acetoacetamide (**6**) and cyclohexanone oxime (**7**). While the reaction displayed promising functionality tolerance in the presence of HFIP, the enantioselectivity of the reaction was negatively affected. Without any HFIP the product was obtained in high selectivity (89% ee). With just 10 equivalents of HFIP, however, the enantioselectivity dropped dramatically (58% ee), and when HFIP was used as the reaction solvent the selectivity dropped further still (15% ee).

To address this poor enantioselectivity a catalyst screen was performed on the benchmark reaction in the presence of varying quantities of HFIP (10 equiv – solvent) to locate a chiral catalyst which maintained high selectivity even when HFIP is used as solvent. Many chiral catalysts were examined but they tended to perform poorly in the presence of HFIP (see SI for details). The results of the four most significant catalysts related to this study are summarized in Table 2. The most broadly successful catalyst for asymmetric cyclopropanation with aryldiazoacetates is Rh_2(*S*-*p*-Ph-TPCP)$_4$ (**9**) but it also suffered from decreasing levels of enantioselectivity on increasing the amount of HFIP.[7, 36, 37] Rh_2(*S*-*tetra*-*p*-BrPhPTTL)$_4$ (**10**), a recently developed catalyst,[38] retained excellent levels of enantioselectivity (98% ee) when up to 10 equiv of HFIP was used, however, when HFIP was used as solvent the enantioselectivity dropped to 72% ee. Unexpectedly, the best catalyst when HFIP is used as solvent is Rh_2(*S*-NTTL)$_4$ (**11**). Previously, Rh_2(NTTL)$_4$, has not shown much promise as a chiral catalyst for the reactions of aryldiazoacetates, and indeed the cyclopropanation in the absence of HFIP resulted in only 36% ee. In this case, however, the enantioselectivity improved with increasing amounts of HFIP and when HFIP was used as solvent, the cyclopropane (**2**) was obtained with 90% ee. The origin of these changes in enantioselectivity is not well understood. ^{1}H NMR studies were conducted in D_2-HFIP to determine whether hydrogen-bonding interactions between HFIP and Rh_2(*R*-NTTL)$_4$ changes it's highly symmetric structure, leading to the observed enhancement in enantioselectivity, however, the spectra of this catalyst in D_2-HFIP matched that of the spectrum in $CDCl_3$ (see SI for details). In future studies, computational studies will be performed to try and identify the origins of the changes in selectivity observed when HFIP is used in combination with different dirhodium tetracarboxylate catalysts.

Table 1: Benchmark reaction of 1-hexene in the presence of various reaction poisons and Rh_2(*R*-TPPTTL)$_4$.

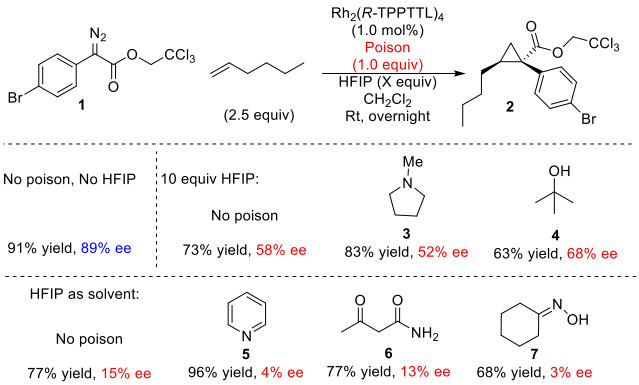
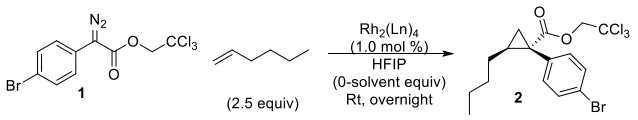
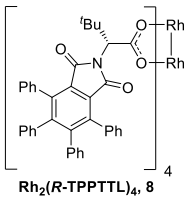


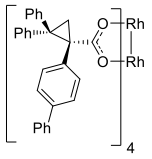
Table 2: Catalyst screen to optimize the enantioselectivity of 1-hexene cyclopropanation in the presence of HFIP.[35-38]





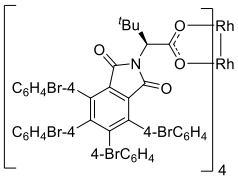
Rh_2(*R*-TPPTTL)$_4$, 8

No HFIP: 89% ee
10 equiv HFIP: 58% ee
HFIP as solvent: 15% ee



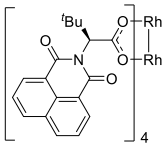
Rh_2(*R*-p-Ph-TPCP)$_4$, 9

No HFIP: 98% ee
10 equiv HFIP: 90% ee
HFIP as solvent: 49% ee



Rh_2(*S*-*tetra*-*p*-BrPhPTTL)$_4$, 10

No HFIP: -98% ee
10 equiv HFIP: -98% ee
HFIP as solvent: -72% ee



Rh_2(*S*-NTTL)$_4$, 11

No HFIP: 36% ee
10 equiv HFIP: 71% ee
HFIP as solvent: 90% ee

(-) %ee denotes that the opposite enantiomer of **2** from that shown in the scheme was obtained. Major enantiomer was determined by analogy to the crystal structure of **110** (CCDC 2182302) obtained in this study along with previous literature reports.[7, 37]

The two most promising catalysts were then applied towards reactions involving several different additives in a high-throughput screen. To avoid the problematic volatility of CH_2Cl_2 on such small scale, the reactions were conducted in $(MeO)_2CO$, a high boiling, environmentally benign solvent which retains high enantioselectivity in these types of cyclopropanations.[37] 90 different poisonous additives were divided into categories based on chemical structure and mode of reactivity (Table 3). These included aromatic heterocycles (**5**, **12-30,** Table 3a), oxygen nucleophiles (**31-39**, Table 3b), nitrogen nucleophiles (**3**, **40-45**, Table 3c), reactive O–H bonds (**4, 7, 46-53**, Table 3d), reactive N–H bonds (**6, 54-72**, Table 3e), sulfur containing compounds (**73-83,** Table 3f), phosphorous containing compounds (**84-87**, Table 3g), and some miscellaneous compounds (**88-95**, Table 3h). Each additive was assessed according to three reaction protocols: Rh_2(*S*-*tetra*-*p*-BrPhPTTL)$_4$ as catalyst with no HFIP, Rh_2(*S*-*tetra*-*p*-BrPhPTTL)$_4$ as catalyst with 10 equiv of HFIP, and Rh_2(*R*-NTTL)$_4$ as catalyst with HFIP as solvent. The conditions which yielded optimal results are reported for each compound and can be identified by color coding. Blue color indicates that no HFIP was needed. Green means that 10 equiv of HFIP was required, whereas orange means HFIP had to be used as solvent to avoid interference from the added poison. In general, when HFIP was used as solvent the reaction displayed the broadest functionality tolerance. Reactions that provided ≥30% yield were deemed successful, and several additives were also examined on laboratory scale (0.10 mmol scale) to validate the results.

The development of general procedures to conduct asymmetric cyclopropanation that would be compatible to a wide variety of heterocycles, would greatly increase the pharmaceutical relevance of rhodium-catalyzed cyclopropanation chemistry.[13, 14] While our earlier work on the cyclopropanation of aza-heterocycles sought to address this need, all of the heterocyclic substrates required substitution adjacent to the nitrogen to reduce its nucleophilicity in order to ensure an effective transformation.[7, 8, 39] Of the 20 aromatic heterocycles examined in this work, only benzothiophene (**12**) was tolerated without the use of HFIP. With 10 equiv of HFIP several heterocycles could be tolerated including strong nucleophiles like oxazole (**14**), DMAP (**16**), and caffeine (**17**). Tolerance to diverse heterocycles was vastly increased when HFIP was used as the reaction solvent. Under these conditions, all 20 of the aromatic heterocycles could be tolerated including pyridine (**5**), several diazines including pyrimidine (**18**) and pyrazine (**20**) and indole (**26**) was also tolerated despite the presence of a reactive N–H bond, along with imidazole (**27**) and triazole (**29**) although the latter caused a reduction in the observed enantioselectivity of the reaction. More complex systems were also compatible with the method including 1,3,5-triazine (**25**), the nucleobase uracil (**30**), isoquinoline (**24**), and several hydroxypyridines (**15**, **21**, and **22**, Table 3a).

Oxygen nucleophiles are often compatible with dirhodium chemistry.[37, 39] Indeed the solvent used for these transformations, $(MeO)_2CO$, and ethyl acetate can even improve the enantioselectivity of these reactions.[37, 40] There is, however, a strong propensity for carbonyls to form ylides with the rhodium carbene, an effect which has been historically exploited in a wide array of important transformations.[41-45] In this study, good reactivity was generally observed with oxygen nucleophiles at low levels of HFIP (Table 3b). Substrates including acetone (**32**), nitromethane (**33**), and phenylisocyanate (**34**) were all tolerated without the use of HFIP. However, more nucleophilic compounds, like *N,N'*-dimethylformamide (DMF, **39**) required 10 equiv HFIP to ensure compatibility. Additionally, some substrates like THF (**36**) and aldehydes (**35** and **37**) can undergo competitive reactions with the carbene including C–H insertion[46] and epoxidation,[47, 48] however these side-reactions were shut down in the presence of 10 equiv HFIP.

Basic nitrogen nucleophiles are known to strongly coordinate to many organometallic catalysts. This poses a serious problem for the dirhodium chemistry as not only can nitrogen coordination prevent carbene formation, but the nitrogen can also react strongly with the carbene to generate an ylide which goes on to do other reactions including the Stevens rearrangement.[41, 49, 50] Indeed, none of the amines tested were tolerated without the use of HFIP with the exception of the bulky tertiary amine triethylamine (**40**). Less bulky and more nucleophilic amines including *N*-methyl pyrrolidine (**3**) and quinuclidine (**45**), required 10 equiv HFIP to be deactivated. Imines like 1,8-diazabicyclo (5.4.0)undec-7-ene (DBU, **42**) and *N,N'*-diisopropyl carbodiimide (DIC, **44**) were also well tolerated under these conditions (Table 3c).

Alcohols and other substrates bearing reactive O–H bonds are well known to insert into metallo-carbenes. Indeed, there is a rich literature around the synthesis of ethers and acetates via this method.[51-59] Unsurprisingly, all of the alcohol substrates reacted with the carbene in the absence of HFIP. Fortunately, several compounds including *tert*-butanol (**4**), salicylic acid (**46**) and acetic acid (**47**) required the use of just 10 equiv HFIP for deactivation. With larger quantities of HFIP, more reactive nucleophiles including primary and secondary alcohols (**48-51**), water (**50**), and phenol (**51**) could also be tolerated. Under these conditions even poly-hydroxylated compounds like ribose (**52**) could be tolerated along with hydroxylamines including cyclohexanone oxime (**7**) and benzohydroxamic acid (**53**, Table 3d).

Reactive N–H bonds are even more challenging to deactivate.[60] Not only can small amines coordinate to the dirhodium catalyst, but

the reactive nitrogen can also react with the carbene. The resulting ylide can go on to conduct a multitude of transformations, including 2,3-sigmatropic rearrangements and N–H insertion.[4, 61-71] None of the additives tested could be tolerated in the absence of HFIP and led to a multitude of side-products. A few additives like *N*-methyl acetamide (**54**), *N,N'*-di-*p*-tolyl thiourea (**55**), and *D*-proline (**57**) were tolerated with just 10 equiv of HFIP. Fortunately, most of the compounds tested were tolerated with the use of HFIP as solvent. Under these conditions most reactive species were compatible. Primary amides (**6**, **60** and **61**), ureas (**58**, **62**, and **67**), guanidine (**59**), and even amines (**64** and **65**) were well tolerated. Unfortunately, regardless of the conditions used, pyrrolidine (**70**), aniline (**69**), *N*-methyl aniline (**71**), and diphenyl hydrazone (**72**) exclusively delivered the N–H insertion products (Table 3e).

The highly polarizable nature of the sulfur atom makes it an excellent ligand for metal catalysts and also makes thiols exceptionally reactive in comparison with the oxygen congeners. As a result, such species can both poison the catalyst through nucleophilic coordination or react with the carbene in a similar manner to nitrogen.[64, 67, 72-74] Sulfur also readily forms hypervalent compounds and the atoms directly bound to the sulfur atom can become more reactive as in the case of sulfonic acids and DMSO. Unsurprisingly, sulfur containing compounds proved difficult to deactivate. Only diphenyl-disulfide (**73**) was tolerated without any HFIP and, in-fact, when HFIP was included with this additive both reactivity and solubility suffered, possibly due to cleavage of the disulfide bond in this acidic medium. The use of 10 equiv HFIP was enough to deactivate several sulfur-containing additives including carbon disulfide (**74**) and (+)-camphor sulfonic acid (**76**). Solvent equivalents of HFIP effectively deactivate phenyl-isothiocyanate (**78**), dimethyl-sulfoxide (**79**), and *p*-toluene-sulfonamides (**80** and **81**). Unfortunately, thiols like thiophenol (**82**), and benzyl-thiol (**83**) were not tolerated under any conditions (Table 3f).

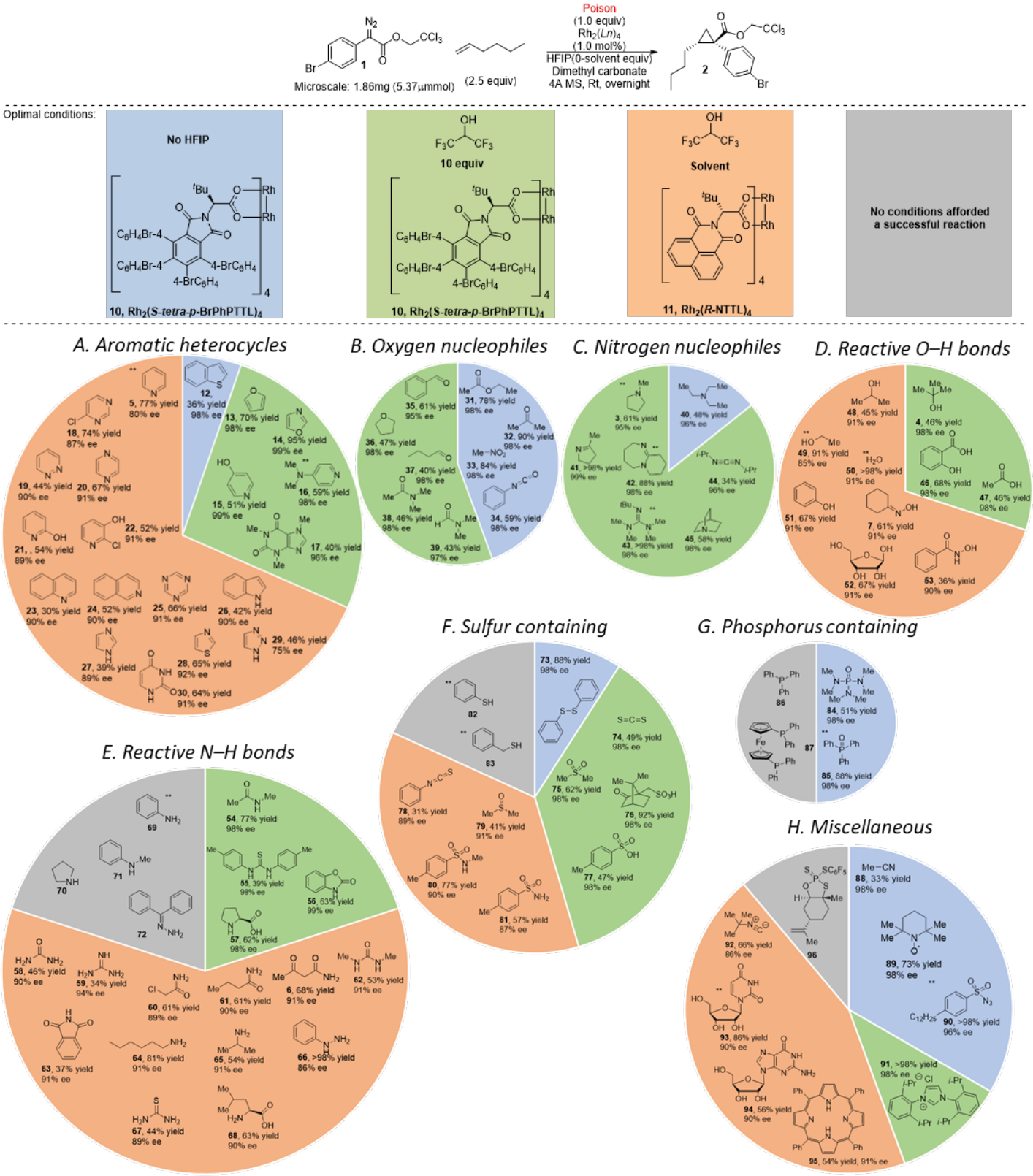
Phosphorus is one of the most important elements in inorganic synthesis due to the soft basic nature of phosphorus making it a strongly coordinating ligand for a large variety of metals.[75] Like, sulfur, phosphorus can exist in a multitude of oxidation states and while P(V) ligands are becoming more popular in catalysis,[76, 77] P(III) ligands are still preferred for a majority of catalytic systems, especially Pd catalyzed cross-coupling.[78-80] The compatibility of phosphorus compounds with this method was highly dependent on the phosphorus oxidation state. P(V) compounds like triphenyl phosphine oxide (**85**) and HMPA (**84**) were well tolerated without the need for any HFIP. The strongly coordinating P(III) species like PPh_3 (**86**) and dppf (**87**), however, were not tolerated under any conditions due to coordination to the dirhodium catalyst, preventing carbene formation.

Various additives were also examined that did not fit neatly into the other categories. While acetonitrile (**88**) is a strongly coordinating solvent, it has been used for a wide array of reactions involving dirhodium nitrenes.[17, 81] While these reactions are generally run at high temperature, the use of acetonitrile suggests that coordination of this ligand is kinetically dynamic. In rhodium carbene chemistry nitriles can cause a drop in yield,[37] but it appears not to react with the carbene when in competition with the cyclopropanation and was tolerated without the need for HFIP. The radical reagent TEMPO (**89**), was also tolerated, it is possible that the singlet nature of the dirhodium carbene prevents modes of radical reactivity and that blue light generation of the carbene would not tolerate TEMPO.[82]

Dodecylbenzene sulfonyl azides (**90**) were also tolerated without the use of HFIP although enantioselectivity suffered as a result. An *N*-heterocyclic carbene ligand (**91**) required the use of 10 equiv HFIP to affect deactivation and gratifyingly strongly coordinating *tert*-butyl isocyanide (**92**) was also tolerated with solvent quantities of HFIP. Several complex molecules, including the nucleosides uridine (**93**) and guanosine (**94**) were compatible under this reaction system and even *meso*-tetraphenylporphyrin (**95**) was well tolerated when HFIP was used as the reaction solvent (Table 3h). Unfortunately, the recently disclosed PSI-reagent (**96**) from the Baran group[83] was not tolerated under any conditions, instead reacting with the carbene either through the nucleophilic sulfur atom or the terminal alkene on the limonene-derived molecule.

While most of the additives tested had little to no impact on the enantioselectivity of the reaction some additives, like 1,2,3-triazole (**29**) and pyridine (**5**), caused a significant reduction in enantioselectivity. This could be due to incomplete deactivation of the nucleophile or coordination of the nucleophile-HFIP complex to the catalyst. While not strong enough to completely poison the reaction, coordination of the nucleophile to the bottom (*tert*-butyl side) rhodium face of the rhodium-carbene complex could cause a change in catalyst structure leading to the observed reduction in enantioselectivity.[7] More work is needed both to understand the effect of HFIP and combinations of HFIP and nucleophile on catalyst stereoselectivity.

Table 3: High-throughput exploration of benchmark reaction tolerance of 90 unique coordinative and reactive poisons



Products are highlighted under the conditions by which best results were obtained in terms of yield and enantioselectivity. Products in blue give optimal results under condition A: Rh_2(*S-tetra-p*-BrPhPTTL)$_4$ (1.0 mol%) and dimethyl carbonate as solvent (80ul, 67mM). Products highlighted in green give optimal results under condition B: Rh_2(*S-tetra-p*-BrPhPTTL)$_4$ (1.0 mol%) and dimethyl carbonate as solvent (80ul, 67mM) with HFIP (10 equiv). Products highlighted in orange give optimal results under condition C: Rh_2(*R*-NTTL)$_4$ (1.0 mol%) and HFIP as solvent (80ul, 67mM). Products highlighted in grey were not tolerated under any conditions giving 0-29% yield of the desired product on both micro and laboratory scale. ** This reaction performed on 0.10 mmol scale without molecular sieves and CH_2Cl_2 or HFIP as solvent.

The results of this study may be visualized in a succinct manner through the use radar plots inspired by Glorius.[84] In these diagrams, the percentage total additives tested from each category which gave successful reactions under the given condition is plotted as a black line. The radar plot is color coordinated to visually display the tolerance of each category. Lines within the red/orange regions then the reaction displays poor functionality tolerance (10-50% of additives tested) and if the line lies within the yellow-green region then the reaction tolerates a wide array of different scaffolds with this functionality (75-100% of additives tested). From this visualization the impact of increasing equivalents of HFIP is made clear as the tolerance map expands toward the edges of the diagram, tolerating 90% of all additives tested when HFIP is used as solvent (81 out of 90, Figure 3).

These results demonstrated a broad array of functionality tolerance. The deactivating effect of HFIP can even be visually observed (Figure 4) in the case of *N*-methyl pyrrolidine (**3**). Without any additive, the dissolved catalyst **10** appears as a green solution (Figure 4a) but upon addition of **3** a distinct color change is observed, and the solution becomes pink (Figure 4b) due to solvatochromism upon coordination of nitrogen to **10**.[85] When HFIP (10 equiv) is added to the solution, another abrupt color change is observed, and the solution becomes a greenish blue coloration (Figure 4c). This indicates that the catalyst is no longer coordinated to **3**, and the catalyst **10** is liberated to perform the desired carbene reaction. Upon the addition of diazo compound **1**, the solution briefly becomes yellow and nitrogen gas rapidly evolves (Figure 4d). After 30 min, the solution reverts to the bluish green of the HFIP solvated catalyst, the diazo compound has been fully consumed and the cyclopropane generated (Figure 4d-e).

After exploring the tolerance of this methodology, a systematic study was conducted to determine if the optimized reaction conditions were capable of high asymmetric induction in the cyclopropanation with a range of aryl-and heteroaryldiazoacetates with various alkenes (Table 4). The results of the Rh_2(*S-tetra-p*-BrPhPTTL)$_4$ - catalyzed reaction and 10 equiv HFIP is indicated in green and the Rh_2(*R*-NTTL)$_4$- catalyzed reaction with HFIP as solvent is indicated in orange. The reactions with Rh_2(*S-tetra-p*-BrPhPTTL)$_4$ tended to give high selectivity regardless of substrate, whereas reactions with Rh_2(*R*-NTTL)$_4$ exhibited more variable levels of enantioselectivity (71-99% ee). All of the products were obtained with the typically high >20:1 d.r observed with rhodium-catalyzed cyclopropanation with the exception of **110**, which was obtained in 7:1 d.r. The major diastereomer of **110** is identified as the *E*-cyclopropane due to the considerable shielding of the silyl-methylene by the *cis*-phenyl ring (appearing at -0.47 ppm). One particularly interesting example is the reaction of methyl 2-(4-pyridyl)-2-diazoacetate with 1-hexene to form **99**, as the reaction cannot proceed without the use of HFIP as solvent.

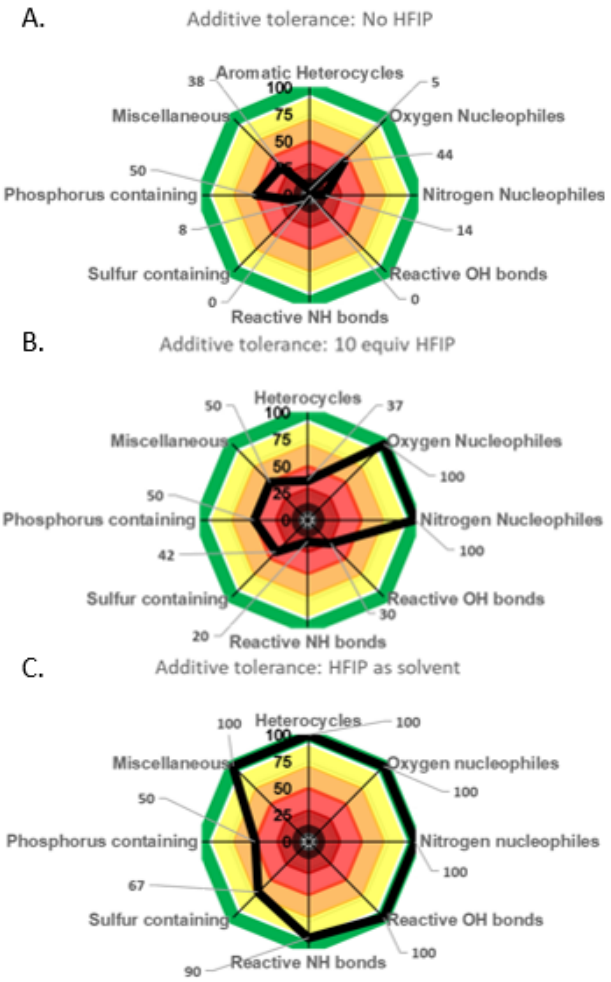


Figure 3. Modified Glorius diagrams visualize the tolerance of the described methodologies to the different classes of poisonous and reactive nucleophiles tested. The values listed represent the percentage of substrates tested that were tolerated with each set of conditions. A: Reactions conducted without HFIP. B: Reactions conducted with 10 equiv HFIP. C: Reactions conducted in HFIP as solvent.

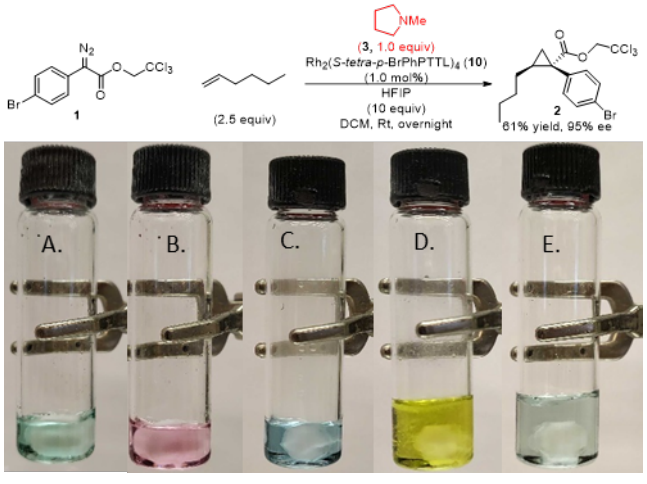
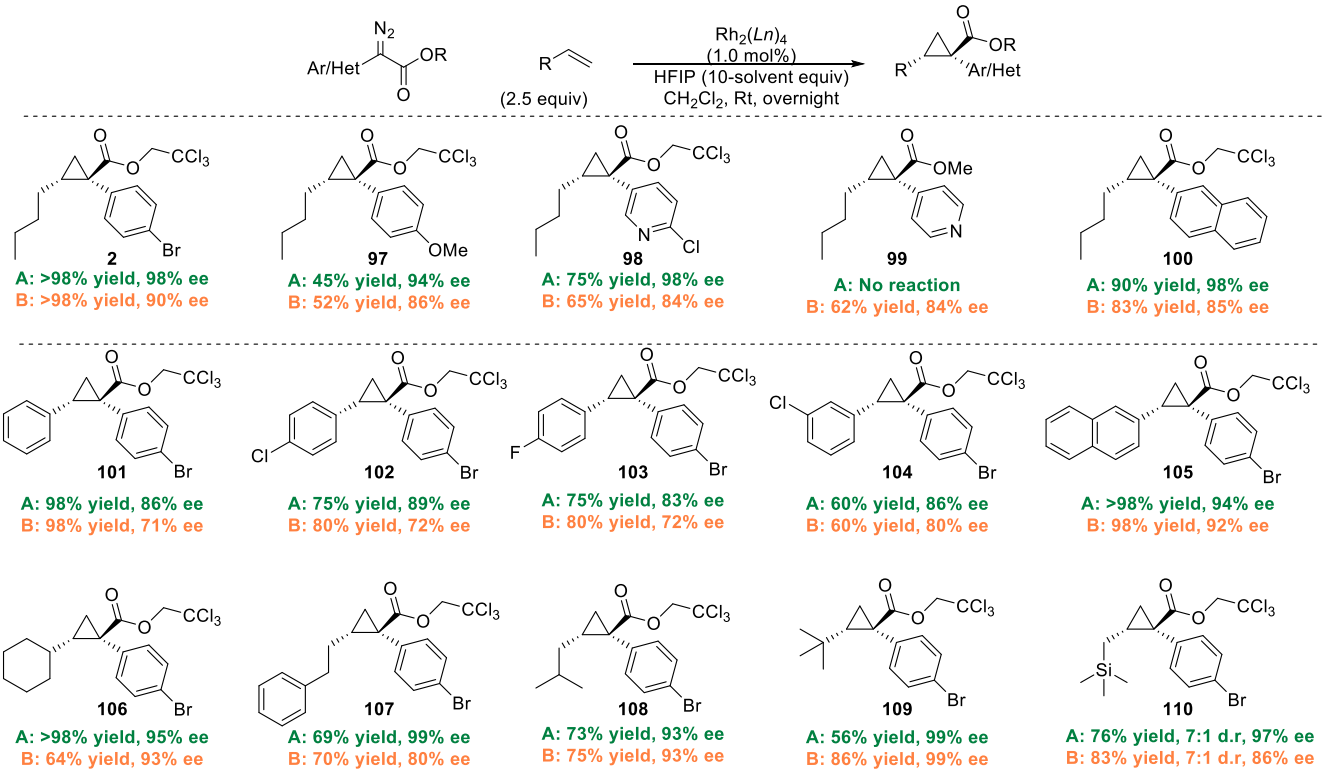


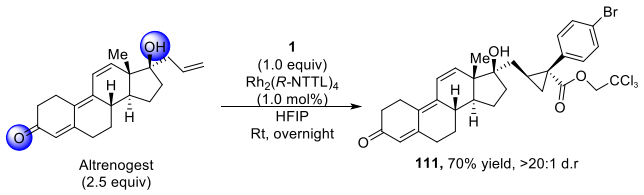
Figure 4: HFIP deactivating a nucleophile in real time. A: The catalyst **10** dissolved in CH_2Cl_2. B: Solution after addition of **3** (1.0 equiv). C: Solution after addition of HFIP (10.0 equiv). D: Solution immediately after addition of **1** (1.0 equiv). E: Solution after stirring at Rt for 30 mins.

Table 4: Scope of aryl/heteroaryl diazoacetates and olefins tolerated under the complementary methodologies described in this work.



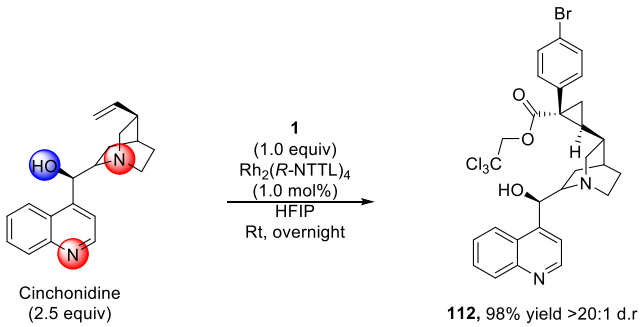
All reactions were conducted at 0.10 mmol scale with 2.5 equivalents of olefin and 1.0 equiv of aryl/heteroaryl diazoacetate in the presence of rhodium catalyst (1.0 mol%) and HFIP. All products were produced in >20:1 d.r. unless indicated. Condition A: Rh_2(*S-tetra-p*-BrPhPTTL)$_4$ 10 equiv HFIP. Condition B: Rh_2(*R*-NTTL)$_4$ HFIP as solvent. Major enantiomer configuration is assigned by analogy to the absolute configuration of **110** determined by X-ray crystallography (CCDC 2182303).

Given the breadth of functionality tolerance the transformation was conducted on several substrates bearing classically poisonous functionality. One of the cleanest transformations occurred with the pharmacologically active progestin Altrenogest (Scheme 2).[86, 87] Without HFIP, the reactive alcohol can selectively react with the carbene and the α-β unsaturated ketone could generate ylides, leading to epoxide and other side-product formation. Fortunately, when HFIP was used as solvent, the compound reacted exclusively at the terminal alkene to afford the desired cyclopropane **111** in 70% yield and with >20:1 d.r. The stereochemical configuration of the cyclopropane is assigned assuming the same preferences for *E*-cyclopropane formation and asymmetric induction seen in the model substrates in Table 4.



Scheme 2: Cyclopropanation of Altrenogest

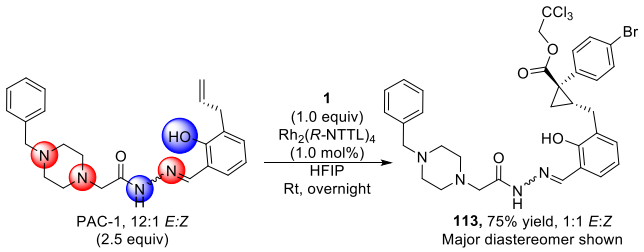
Cinchona alkaloids are an important class of molecules with a wide variety of pharmaceutical and industrial applications.[88, 89] (*S*)-Cinchonidine features several problematic functionalities including a chiral secondary alcohol which could react with the carbene (Scheme 3). The molecule also features several poisons including a quinoline, and a quinuclidine ring which coordinates to the catalyst, preventing rhodium carbene generation in the absence of HFIP. Once the reaction was performed in HFIP as solvent with Rh_2(*R*-NTTL)$_4$ as catalyst the desired cyclopropane **112** was afforded as in 98% yield and with >20:1 d.r. Although 2.5 equiv of the complex alkene is required for high yield, unreacted starting material was recovered quantitatively during purification. The stereochemical configuration of the cyclopropane was initially assigned assuming the same preferences for *E*-cyclopropane and asymmetric induction seen in the model substrates in Table 4, and this was confirmed via X-ray crystallography (CCDC 2182287).



Scheme 3: Cyclopropanation of (*S*)-Cinchonidine

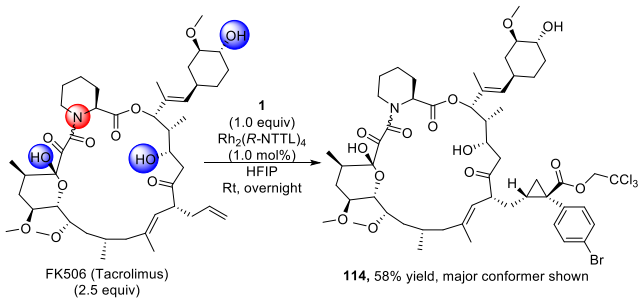
The procaspase-3-activator, PAC-1,[90] was also successful in the reaction and bares a significant amount of problematic functionality including a hydrazide, piperazine, and an unprotected phenol which results in undesired side-reactions in the absence of HFIP (Scheme 4). While the transformation occurred at the free alkene as intended using HFIP as solvent, the acidity of the solvent scrambled the *E:Z*

ratio of the of the hydrazide. The starting material displayed a 12:1 ratio between these isomers, the product **113** was isolated as a 1:1 mixture that we were unable to separate by HPLC. The stereochemical configuration of the cyclopropane is assigned assuming the same preference for *E*-cyclopropane formation and asymmetric induction seen in the model substrates in Table 4. This assignment is further bolstered by the appearance of the minor diastereomer of both the *E* and *Z* isomer methylene at a higher chemical shift (2.75 ppm) than the major product methylene (2.65 ppm). This is due to the shielding experienced by the methylene in the *E*-cyclopropane diastereomer which is absent in the *Z*-cyclopropane. Interestingly, while one of the isomers gives poor diastereoselectivity (6:1 favoring the *E*-cyclopropane), the other isomer gives the typically high diastereoselectivity observed in this work (>20:1 d.r again favoring the *E*-cyclopropane). Due to the complexity of the spectrum, it was not possible to determine whether the *E* or *Z*-hydrazide afforded the highest diastereoselectivity.



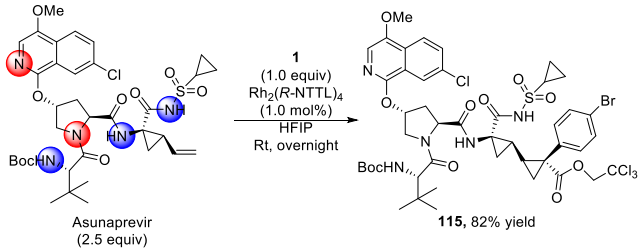
Scheme 4: Cyclopropanation of PAC-1

Tacrolimus, or FK-506, is an important calcineurin inhibitor.[91, 92] The molecule is a large macrocycle consisting of 21 atoms and bearing a variety of problematic functionality including a three free hydroxyl groups and piperidinyl amide which could react with the carbene (Scheme 5). The molecule exists as a dynamic mixture of conformers in solution corresponding to *cis/trans* isomerization around the piperidinyl amide and is used medicinally as this mixture. Fortunately, both conformers were reactive under the optimized conditions, and only cyclopropanation of the free alkene was observed. No rearrangement of the macrocyclic core was observed despite the acidic reaction conditions and the identity of the product **114** was confirmed via 2D NMR experiments. The stereochemical configuration of the cyclopropane is assigned assuming the same preference for *E*-cyclopropane formation and asymmetric induction seen in the model substrates in Table 4. The diastereoselectivity of this product was not possible to determine due to the complexity of this conformationally dynamic macrocycle. The cyclopropane and methylene signals that are often indicative of the diastereoselectivity are buried underneath the many alkyl signals of the large molecule and further convoluted by the presence of 2 major conformations of the piperidinyl amide in solution, making reliable determination of diastereoselectivity impossible.



Scheme 5: Cyclopropanation of FK506(Tacrolimus)

The hepatitis-C drug Asunaprevir[93, 94] was also successfully cyclopropanated to afford **115** (Scheme 6). The highly complex scaffold features a diverse array of functionality including a quinoline, a pyrrolidinyl amide, a sulfonamide and a *Boc*-protected *tert*-leucine residue. In the absence of HFIP, the isoquinoline heterocycle could poison the rhodium catalyst or one of the secondary amido nitrogens could preferentially insert into the carbene. Fortunately, when HFIP was used as solvent, only cyclopropanation of the terminal olefin was observed, and the structure was confirmed by 2D NMR, although the resultant product was unstable at elevated temperatures. The use of an acidic reaction medium and TFA as a mobilizing additive in the subsequent HPLC purification led to partial removal of the *Boc*-group. As a result, this compound was not obtained with high purity though it was still possible to confirm the structure of the major product through 2D NMR experimentation. The stereochemical configuration of the cyclopropane is assigned assuming the same preference for *E*-cyclopropane formation and asymmetric induction seen in the model substrates in Table 4. This is bolstered by the significant shielding of the diastereotopic cyclopropane methylene adjacent to the site of carbene insertion. In the starting material these signals appear at 1.98 and 1.49 ppm, but in the product, they are no longer close to an alkene and are also significantly shielded by the *p*-bromophenyl appearing at 0.66 and 0.45 ppm. This shielding is only present in the *E*-cyclopropane suggesting that the reaction occurs with the high diastereoselectivity typically observed in this reaction although the minor diastereomer signals could not be confidently assigned due to the complex nature of the NMR.



Scheme 6: Cyclopropanation of Asunaprevir.

Conclusion

The ability of HFIP to selectively deactivate coordinative poisons and desensitize rhodium carbenes to highly reactive substrates has been leveraged to effect highly enantioselective cyclopropanation in the presence of a myriad of poisonous and reactive functionalities. The methodology is applicable to substrates bearing reactive functionality including complex APIs and natural products. This simple additive enables broad functionality tolerance for rhodium carbene transformations making it a more useful tool for accessing chiral molecules and diversifying medicinally relevant scaffolds. Future efforts will be centered around expanding this methodology to include other rhodium carbene reactions including functionalization of C–H bonds, and the broader applicability of HFIP for desensitizing other metal catalyzed processes to poisonous nucleophiles.

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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). The other authors have no competing financial interests.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Complete experimental procedures, and compound characterization are described in the Supporting Information. (PDF)

Accession Codes

CCDC 2182302 and 2182287 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 902 1223 336033.

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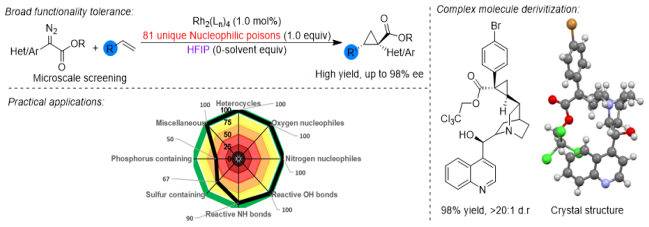
TOC Graphic


Broad functionality tolerance:
Rh2(Ln)4 (1.0 mol%)
81 unique Nucleophilic poisons (1.0 equiv)
HFIP (0-solvent equiv)
Het/Ar
OR
Microscale screening
High yield, up to 98% ee
Practical applications:
Heterocycles
Oxygen nucleophiles
Nitrogen nucleophiles
Reactive OH bonds
Reactive NH bonds
Sulfur containing
Phosphorus containing
Miscellaneous
Complex molecule derivitization:
98% yield, >20:1 d.r
Crystal structure