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Regio- and Diastereoselective Access to Fused Isoxazolidines via Ru(II)-Catalyzed C−H Activation of Nitrones and Coupling with Perfluoroalkylolefins

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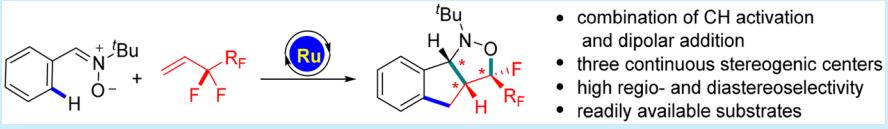
Supporting Information



ABSTRACT: The synthsis of fluorinated isoxazolidines in bicyclic settings has been realized via Ru(II)-catalyzed C−H activation of aryl nitrones with perfluoroalkyl-substituted olefins as the coupling partner. The reaction proceeded via initial chelation-assisted C(aryl)−H allylation followed by regio- and diastereoselective intramolecular dipolar addition between the nitrone directing group and the olefin unit.

1,3-Dipolar cycloadditions (1,3-DC) provide a prominent method for the rapid assembly of five-membered heterocycles, and their utility spans every aspect of chemistry, including total synthesis, material synthesis, and pharmaceutical chemistry.[1] 1,3-DC of nitrones,[2] one of the most well-studied 1,3-dipoles, represents an efficient strategy to access isoxazolidines,[3] which are privileged scaffolds with a diverse array of biological activities including antifungal,[4b] anticancer,[4f] and anti-inflammatory activities,[4g] among others (Figure 1).[4] In addition, isoxazolidines

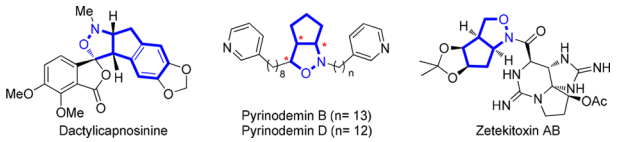
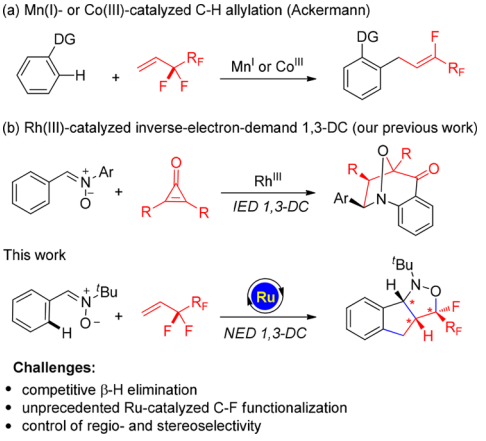


Figure 1. Representative biologically active isoxazolidine scaffolds.

are also valuable masked synthetic intermediates and chiral ligands in asymmetric catalysis.[5] While a broad spectrum of methods have been established for isoxazolidine synthesis, it is necessary to explore 1,3-DC that are integrated with other important transformations in a tandem process, which may serve to deliver useful scaffolds with molecular complexity in a concise and step-economic fashion.

Introduction of a fluorine or fluorine-containing fragments into organic molecules usually gives rise to unique biological and physical properties, thus facilitating lipid solubility, metabolic stability, and binding properties to biological targets.[6] In particular, various compounds with a fluorinated quaternary stereocenter[7] are among the best-selling pharmaceuticals. Hence, substantial efforts have been devoted to expeditious synthesis of these structures.[7c,d] It has been extensively demonstrated that metal-catalyzed C−H activation of arenes has shown distinct superiorities for assembly of complex heterocycles.[8] In particular, Ru(II) complexes have received increasing attention in catalytic C−H functionalization of arenes with high reactivity and cost-effectiveness.[9] However, the development of robust and operationally simple ruthenium(II)-catalyzed systems for C−F functionalization in the context of C−H activation remains largely underexplored.[10] Recently, Loh and co-workers applied fluorinated styrenes as coupling partners for monofluorolefination of arenes,[10c] where the C−F bond cleavage occurred selectively via β-F elimination. Ackermann elegantly reported the coupling of various arenes with perfluoroalkylalkenes via C−H activation, leading to direct allylation of arenes (Scheme 1).[10d,e] We[11] recently reported Rh(III)-catalyzed C−H activation of

Scheme 1. Coupling of Nitrone and Alkenes via C−H Activation



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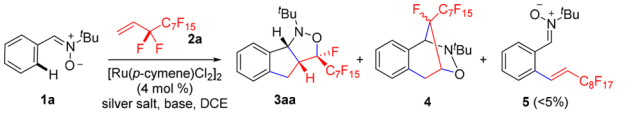
nitrones[12] in the coupling with cyclopropenones, where C−H acylation occurred first to deliver an enone dipolarophile for subsequent intramolecular 1,3-DC with the nitrone. Inspired by Ackermann's studies[10d,e] and as a continuation of our interest in Ru(II)-catalyzed C−H activation,[13] we aim to develop efficient methods to access heterocycles bearing fluorinated quaternary stereocenters by integration of 1,3-DC into Ru(II)-catalyzed C−H activation. We rationalized that the following challenges should be addressed: (1) β-F elimination from Ru(II) has not been reported in C−H activation systems and control of the Z/E selectivity of the newly formed C═C bond via β-F elimination remains challenging,[10d,e,14] which will eventually affect the diastereoselectivity of the 1,3-DC. (2) It remains a big challenge whether high levels of regio- and stereocontrol of the 1,3-DC are realizable since the product contains three stereogenic centers. We now report a concise and redox-neutral strategy to access fluorinated bicyclic isoxazolidines via Ru-catalyzed C−H activation (Scheme 1).

The coupling of *N-tert*-butyl nitrone **1a** and perfluoroalkylalkene **2a** was chosen as the model reaction (Table 1). It was found that a ruthenium catalyst exhibited superior reactivity and selectivity when compared to the Rh, Co, and Mn catalysts (see the Supporting Information). No coupling products were detected in the absence of silver additive or base (entries 1 and 2). In many cases, three products (**3aa**, **4**, **5**) were generated as a result of different regio- and chemoselectivity, with **3aa** being the major product (entry 3). Product **3aa** was fully characterized as a fused isoxazolidine, and it was likely generated via a sequence of C−H allylation and intramolecular normal-electron-demand (NED) 1,3-DC. The yield was dramatically improved to 93% using DCE as a solvent. Unfortunately, the ratio of **3aa**/**4** was only moderate, and these two products are hardly separable. The selectivity of **3aa** versus **4** corresponds to different regioselectivity (normal-electron-demand versus inverse-electron demand (IED)) with respect to the 1,3-DC.[15] Higher yields but lower regioselectivity were obtained at a lower reaction temperature (entries 6−8). The silver additives had a significant impact on the regioselectivity (entries 9−13), and our base screening returned K_2HPO_4 as a superior one in terms of reactivity and/or selectivity (entries 14−16). High yield and selectivity were eventually realized when mixed silver additives were adopted (entry 17).

With the optimal conditions in hand, we next explored the scope and generality of this coupling system (Scheme 2). *N-tert*-Butyl nitrone bearing both electron-donating and -withdrawing groups at the *para* position all underwent smooth coupling with alkene **2a** to afford the desired products (**3ba**−**ka**) in moderate to excellent yields. The identity of **3ia** was unambiguously confirmed by X-ray crystallography (Figure 2). Nitrones bearing a *m*-Me and *m*-CF_3 group also reacted smoothly in moderate yields (**3la**, **3ma**), and the coupling occurred selectively at the less hindered *ortho* site. Various other *meta*-substituted nitrones were also applicable, but the C−H activation occurred at both *ortho* positions with low to moderate regioselectivities (**3na**−**qa**). Furthermore, *ortho*-substituted nitrones also coupled efficiently (**3ra**−**ua**). Disubstituted nitrones and naphthalene-based nitrones were also suitable substrates and afforded the annulated products in moderate yields (**3va**−**za**). Unfortunately, *N*-cyclohexyl, -benzyl, and -phenyl nitrones failed to undergo efficient coupling. The observation is attributed to the large steric

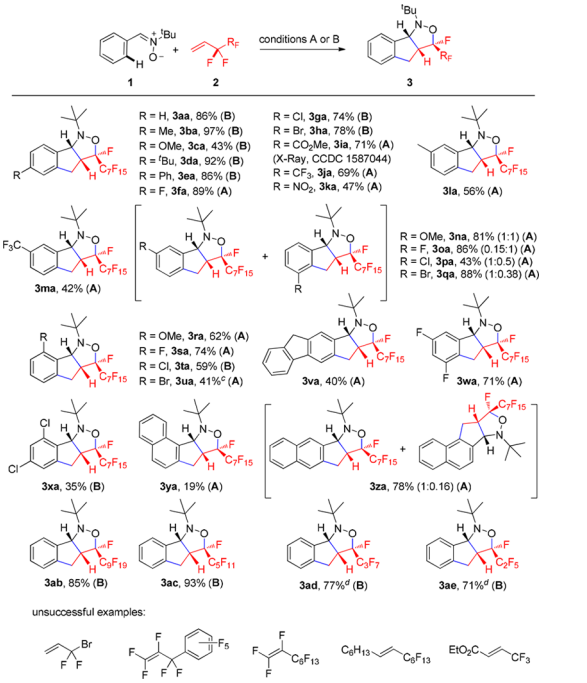
Table 1. Optimization Studies[a]



entry	additive (mol %)	base (1 equiv)	temp (°C)	yield (%)[b] of **3aa** (**3aa**/**4**)[c]
1		K_2CO_3	120	0
2	$AgSbF_6$ (40)		120	<5
3[d]	$AgSbF_6$ (40)	K_2CO_3	120	31 (>30:1)
4	$AgSbF_6$ (40)	K_2CO_3	120	93 (10:1)
5	$AgSbF_6$ (40)	K_2CO_3	140	77 (5:1)
6	$AgSbF_6$ (40)	K_2CO_3	100	74 (10:1)
7	$AgSbF_6$ (40)	K_2CO_3	80	94 (3.3:1)
8	$AgSbF_6$ (40)	K_2CO_3	60	99 (2:1)
9	**$AgSbF_6$ (20)**	**K_2CO_3**	**120**	**89 (10:1)**
10	$AgNTf_2$ (20)	$NaHCO_3$	120	73 (10:1)
11	AgOTf (20)	$NaHCO_3$	120	20 (>30:1)
12	$AgBF_4$ (20)	$NaHCO_3$	120	61 (15:1)
13	$AgPF_6$ (20)	$NaHCO_3$	120	75 (25:1)
14	$AgPF_6$ (20)	Li_2CO_3	120	68 (>30:1)
15	$AgPF_6$ (20)	KH_2PO_4	120	90 (14.3:1)
16	$AgPF_6$ (20)	K_2HPO_4	120	50 (50:1)
17	**$AgPF_6$ (10), $AgSbF_6$ (10)**	**K_2HPO_4**	**120**	**84 (25:1)**

[a]Reaction conditions: nitrone **1a** (0.2 mmol), **2a** (0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (4 mol %), silver additive, and a base (0.2 mmol) in DCE (2 mL) at 60−120 °C under nitrogen for 16 h. [b]Isolated yield after chromatography. [c]The ratio of **3aa**/**4** in the parentheses was determined by ^{1}H NMR spectroscopy. [d]1,4-Dioxane was used as a solvent.

Scheme 2. Scope of the C−H Allylation/1,3-DC[a,b]



[a]Conditions A: **1** (0.2 mmol), **2** (0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (4 mol %), $AgSbF_6$ (20 mol %), K_2CO_3 (0.2 mmol) in DCE at 120 °C under N_2 atmosphere for 16 h. Conditions B: **1** (0.2 mmol), **2** (0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (4 mol %), $AgSbF_6$ (10 mol %), $AgPF_6$ (10 mol %), K_2HPO_4 (0.2 mmol) in DCE at 120 °C under N_2 for 16 h. [b]Isolated yield. The ratio of **3**/**4** is >20:1 in all cases. [c]HFIP solvent was used. [d]Perfluoroalkylalkene (3.0 equiv) was used at 100 °C.

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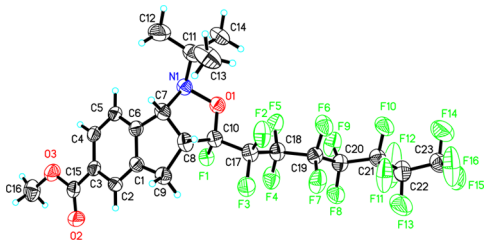
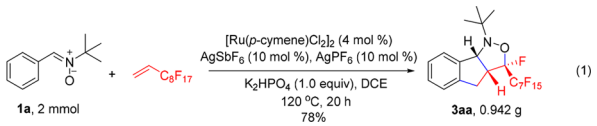


Figure 2. Molecular structure (ORTEP) of **3ia**.

hindrance to might favor the *Z*-configuration of nitrone and facilitate cyclometalation. Furthermore, steric protection will also inhibit hydrolysis of nitrone. The generality of perfluoroalkylalkenes has also been investigated. Various perfluoroalkylalkenes underwent smooth coupling with **1a** in high efficiency (**3ab**−**ae**, 71−93%). Of note, reactions of perfluoroalkylalkenes with a short chain were performed at a lower temperature due to their lower boiling point (**3ad**, **3ae**). In all cases, the fused isoxazolidine products were generated in excellent regio- and diastereoselectivity. The observed normal-electron-demand (NED) coupling is likely caused by the strong electronic effect of the fluoroalkyl chain. This NED coupling also likely occurred via a concerted pathway, which leads to formation of product **3** in a diastereospecific fashion. Unfortunately, no desired products were detected due to electronic or steric effects when other olefins were investigated (Scheme 2).

To demonstrate the scalability of the catalytic system, gram-scale synthesis of **3aa** has been realized in good yield under conditions B (eq 1). A series of experiments were then

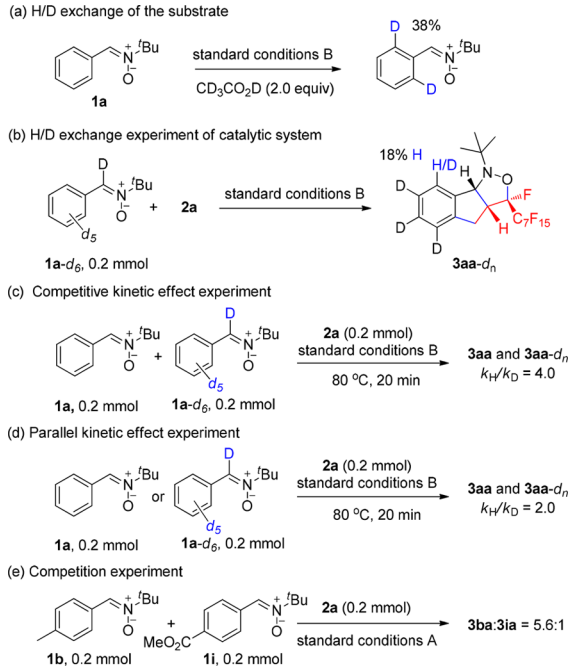


(1)

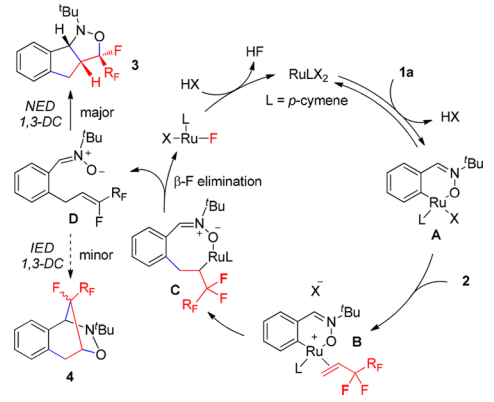
performed to gain mechanistic insight into this coupling system (Scheme 3). To probe the C−H activation process, H/D exchange experiment for **1a** was conducted under conditions B in the presence of CD_3CO_2D. ^1H NMR analysis of the recovered substrate revealed that the *ortho* CH was deuterated (38% D) (Scheme 3a). Furthermore, H/D exchange experiment for **1a**-d_6 was conducted under conditions B in the presence of **2a** (Scheme 3b). ^1H NMR analysis of the product **3aa**-d_n revealed that the *ortho* CD was partially hydrogenated (18% H), suggesting reversibility of the C−H activation. Subsequently, the kinetic isotope effect (KIE) was measured, and KIE values acquired from both intermolecular competition (k_H/k_D = 4.0) and parallel experiment (k_H/k_D = 2.0) using **1a** and **1a**-d_6 suggested that cleavage of the C−H bond is likely involved in the turnover-limiting step (Scheme 3c,d). Moreover, a competitive experiment between two nitrones differing in electronic effects was carried out (Scheme 3e), and the ratio of products (**3ba**/**3ia** = 5.6) suggested that the more electron-rich nitrone exhibits higher reactivity.

On the basis of these results and previous reports,[10d,e,11] a plausible catalytic cycle is proposed in Scheme 4. Cyclometalation of *N*-*tert*-butyl nitrone **1** affords a ruthenacyclic intermediate **A**, to which perfluoroalkylalkene **2** coordinates to give intermediate **B**. An eight-membered ruthenacyclic intermediate **C** was then formed via Ru−C(aryl) migratory insertion into the C═C bond. Subsequently, intermediate **C** undergoes selective *β*-F elimination via a syn-coplanar transition state to

Scheme 3. Mechanistic Studies



Scheme 4. Proposed Mechanism



furnish the allylated intermediate **D**, where the olefinic F and H are *trans*-disposed, together with formation of a Ru(II) fluoride species. Further protonation by HX regenerates the active Ru(II) catalyst for the next catalytic cycle. Normal-electron-demand intramolecular 1,3-dipolar cycloaddition occurs selectively to eventually furnish the annulated product **3**.

In summary, we have developed Ru(II)-catalyzed allylation of nitrone, which sets the stage for subsequent intramolecular 1,3-dipolar cycloaddition. This catalytic system represents a concise process that incorporates *β*-F elimination into C−H activation and cycloaddition system and allows for highly regio- and diastereoselective synthesis of isoxazolidines bearing three contiguous stereogenic centers. Future studies toward applications of ruthenium catalysts in other complex transformations via C−H activation are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03775.

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Detailed experimental procedures, characterization of new compounds, and NMR spectra (PDF)

Accession Codes

CCDC 1587044 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 1223 336033.

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Notes

The authors declare no competing financial interest.

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