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Regio- and stereo-selective construction of *cis*-indeno[1,2-*c*]isoxazoles *via* a C–H allylation/1,3-dipolar cycloaddition cascade†

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Combining rhodium-catalyzed C–H allylation with intramolecular 1,3-dipolar cycloaddition consistently yields bridged [*n*.2.1] isoxazolidines *via* intermediates bearing activated dienophiles. In the current work, this protocol was used to install a non-activated *Z*-alkene unit into the nitrone substrate, resulting in the access of fused *cis*-indeno[1,2-*c*]isoxazoles with excellent regio- and stereo-selectivity levels. A wide scope was demonstrated for nitrones including for those derived from natural products and pharmaceutical molecules. Derivatizations of the representative products were conducted to provide diverse important skeletons.

The isoxazolidine skeleton is one of the most common units in natural products. Molecules containing the unique isoxazolidine scaffold have been widely discovered and investigated for their biological properties (Scheme 1a).[1] Its construction has long been of interest to organic and medicinal chemists. Of the various methods for accessing isoxazoles, the intermolecular 1,3-dipolar cycloaddition (1,3-DC) reaction of nitrones with alkenes has been particularly well developed with good stereocontrol (Scheme 1b).[1a,2] Besides being a good 1,3-dipole, the nitrone moiety has also been revealed to be an outstanding directing group in transition-metal-catalyzed C–H functionalization and cyclization.[3,4] A strategy involving nitrone-directed C–H activation provides a pathway for the installation of an unsaturated fragment into an isoxazole-containing molecule, and may offer the possibility for an intramolecular 1,3-DC reaction (Scheme 1c).[5–9] Our group has achieved a ruthenium-catalyzed C–H fluoro-allylation/normal-electron-demand 1,3-DC reaction for the synthesis of fused isoxazolidines bearing fluorine fragments.[5] However, the combination of rhodium-catalyzed C–H activation of nitrones with subsequent intramolecular 1,3-DC only affords the bridged [*n*.2.1] bicyclic isoxazolidines *via* intermediates, each bearing an electron-deficient or conjugated dienophile.[6–9] Thus, in the current work, we developed a rhodium-catalyzed stereoselective construction of fused tricyclic indeno[1,2-*c*]isoxazoles *via* the nitrone-directed C–H activation/*cis*-selective 1,3-DC cascade (Scheme 1d). The delivered indeno[1,2-*c*]isoxazole products can be easily converted to diverse useful skeletons.[1a,10]

We initiated the cross coupling/cyclization cascade by reacting (*Z*)-*N*-*tert*-butyl-1-phenyl nitrone (**1a**) with 4-vinyl-1,3-dioxolan-2-one (**2a**) (Table 1), which is a common C–H allylation reagent in metal catalysis.[11] To our delight, the desired indeno[1,2-*c*]isoxazole product (**3aa**) was isolated in 64% yield in the presence of $[Cp^*RhCl_2]_2/AgSbF_6$ and Ag_2CO_3 in 1,2-dichloroethane (DCE) at 60 °C (entry 1). The *cis* relationship of three hydrogen atoms in compound **3aa** was confirmed from the results of single-crystal X-ray diffraction (CCDC 2190949†). A ruthenium catalyst was also tested, but was found to be an ineffective as a catalyst for the cascade reaction (entry 2). Including both $[Cp^*RhCl_2]_2$ and $AgSbF_6$ was determined to be necessary for the effectiveness of the catalytic system (entries 3 and 4). A screening of solvents indicated PhCl to be optimal, giving the product with 79% yield (entries 5–9). The reaction also occurred, but with decreased yields, when other additives such as $Cu(OAc)_2$, AgOAc, Na_2CO_3 or NaOAc were used instead of Ag_2CO_3 (entries 10–13). Decreasing the number of equivalents of Ag_2CO_3 slightly improved the reaction efficiency (entry 14). However, a poor yield was found when the reaction was conducted without Ag_2CO_3 (entry 15). Decreasing the number of equivalents of **2a** gave negative results (entries 16 and 17). Increasing the reaction temperature had little effect on the reaction efficiency (entry 18). A similar yield was achieved when the reaction was conducted under air (entry 19).

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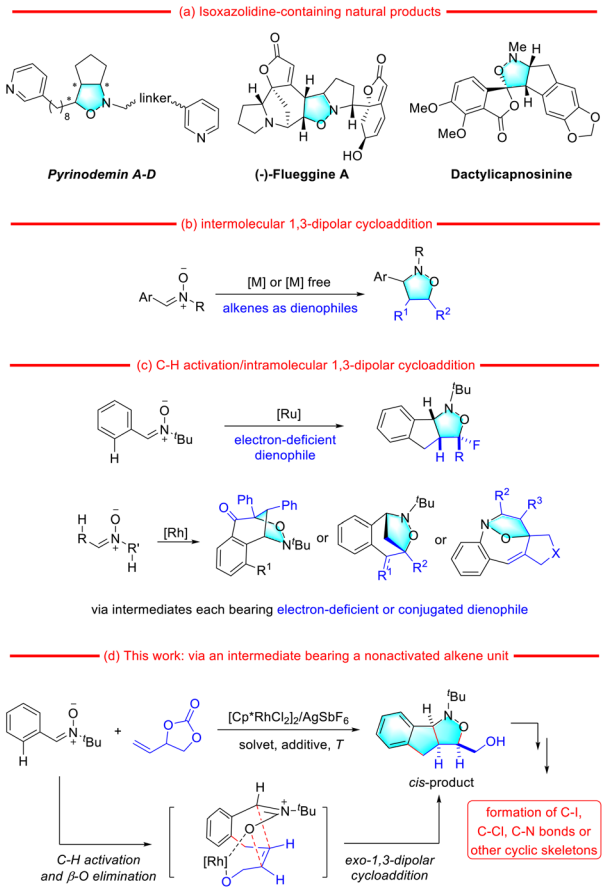
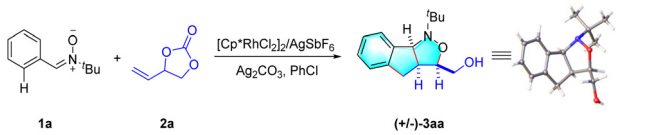


Scheme 1 Construction of isoxazolidines from nitrones.

Table 1 Optimization of the reaction conditions[a]



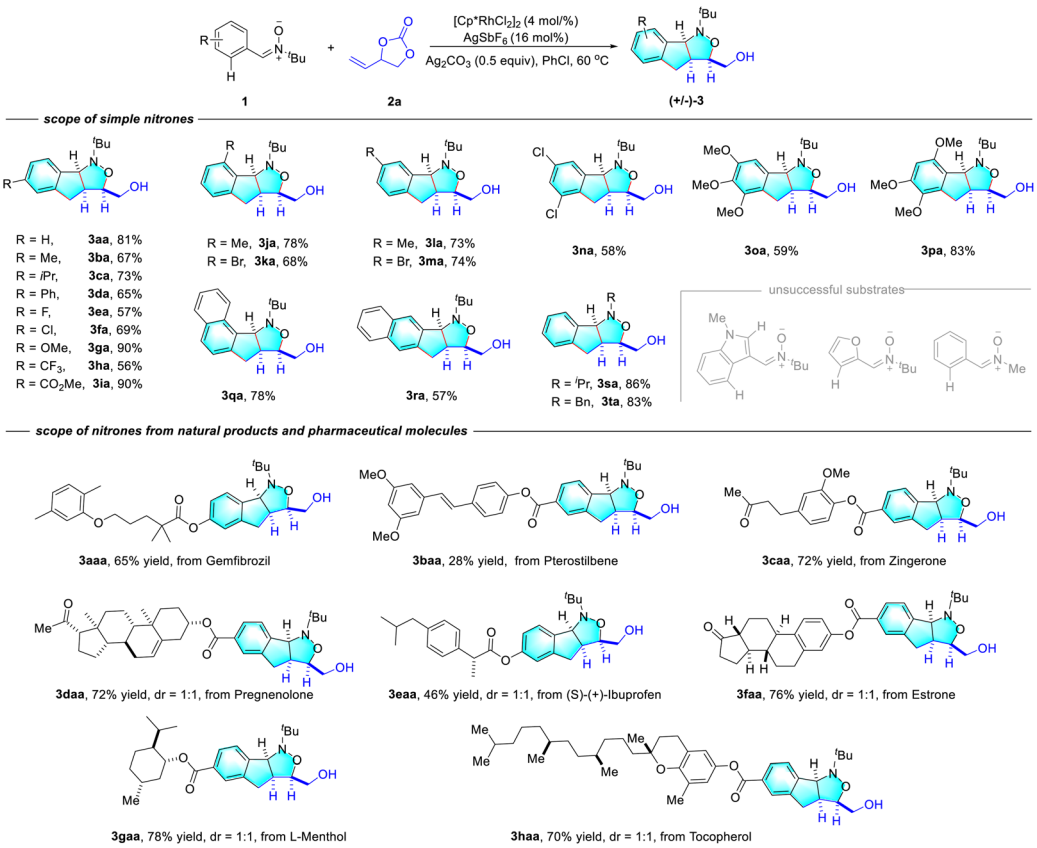
Entry	Additive	Solvent	Yield/%
1	Ag_2CO_3	DCE	64%
2[b]	Ag_2CO_3	DCE	n.r.
3[c]	Ag_2CO_3	DCE	n.r.
4[d]	Ag_2CO_3	DCE	n.r.
5	Ag_2CO_3	DCM	63%
6	Ag_2CO_3	PhCl	79%
7	Ag_2CO_3	CH_3CN	n.r.
8	Ag_2CO_3	Toluene	64%
9	Ag_2CO_3	TFE	36%
10	$Cu(OAc)_2$	PhCl	31%
11	AgOAc	PhCl	40%
12	Na_2CO_3	PhCl	23%
13	NaOAc	PhCl	31%
14[e]	Ag_2CO_3	PhCl	81%
15	—	DCE	23%
16[f]	Ag_2CO_3	PhCl	59%
17[g]	Ag_2CO_3	PhCl	71%
18[h]	Ag_2CO_3	PhCl	78%
19[i]	Ag_2CO_3	PhCl	80%

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), additive (1.0 equiv.), solvent (1.0 mL), 60 °C, 12 h, under Ar, a single isomer was detected unless noted otherwise, n.r. = no reaction. [b] $[CymeneRuCl_2]_2$ instead of $[Cp^*RhCl_2]_2$. [c] Without $AgSbF_6$. [d] Without $[Cp^*RhCl_2]_2$. [e] Ag_2CO_3 (0.5 equiv.). [f] Ag_2CO_3 (0.5 equiv.), **1a : 2a** = 1 : 1. [g] Ag_2CO_3 (0.5 equiv.), **1a : 2a** = 1 : 1.2. [h] Ag_2CO_3 (0.5 equiv.), 80 °C,. [i] Ag_2CO_3 (0.5 equiv.), air.

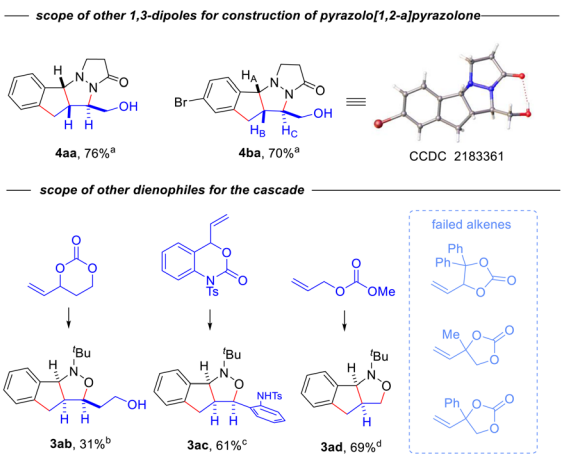
We next investigated the scopes of the reaction cascade with the optimal conditions. As shown in Scheme 2, diverse substituted nitrones were examined and found to be tolerated in the system. Nitrones with *para*-, *ortho*-, or *meta*-substituted phenyl groups all gave the corresponding products with moderate to good yields (**3ba–3ma**, 57–90% yields). Electron-deficient groups (**3ha** and **3ia**), electron-rich groups (**3ga**), hydrocarbyl groups (**3ba–3da**, **3ja** and **3la**), and halogens (**3ea**, **3fa**, **3ka** and **3ma**) were all tolerated in this reaction system. Multi-substituted phenyl nitrones were reacted with the alkene **2a**, and afforded the desired products with acceptable yields (**3na–3pa**, 58–83%). Nitrones from 1-naphthalene carboxaldehyde or 2-naphthalene carboxaldehyde both delivered the corresponding isoxazolidine skeletons (**3qa** and **3ra**, 78% and 57%, respectively). However, nitrones from heteroarylaldehydes such as 1-methyl-1*H*-indole-3-carbaldehyde and furan-2-carbaldehyde failed to participate in the reaction. Different *N*-substituents were also introduced, with a methyl group yielding negative results, and isopropyl and benzyl groups yielding positive results (**3sa** and **3ta**, 86% and 83%, respectively). The catalytic system was applied to realize late-stage functionalization[12] for some important natural products and pharmaceutical molecules. The reaction cascade took place smoothly with poor to good yields (**3aaa–3caa**, 28–72%). However, inseparable diastereomers were afforded with nearly 1 : 1 dr values when the single nitrones derived from enantiotopic bioactive molecules were employed (**3daa–3haa**, 46–78%).

A 1,3-dipolar pyrazolone-onium-salt-type directing group was successfully introduced to access pyrazolopyrazolones (Scheme 3, **4aa** and **4ba**).[13] The configuration of **4ba** was confirmed from the results of single-crystal X-ray diffraction, where the *trans* relationship of H_C with H_A and H_B was found. The formation of the *trans* rather than the above-described *cis* relationship may have been caused by a hydrogen-bonding interaction of the OH group with the C=O group in the intermediate. The interaction was also observed in the final product (**4ba**). Other similar dienophiles were tested, and gave the corresponding isoxazolidine skeletons with different substitutions (**3ab–3ac**). The substituted 4-vinyl-1,3-dioxolan-2-ones gave no product, revealing the sensitivity of the reaction cascade to steric effects.

To further demonstrate the practicality of this reaction system, a scaled-up synthesis of **3aa** was carried out, and was found to do so with good yield (Scheme 4, 5 mmol scale, 72%). Diverse transformations of **3aa** and **3ta** were realized (Scheme 4). Halogenation of **3aa** with I_2 or CCl_4 in the presence of PPh_3 gave the corresponding iodide or chlorinated products (**5** and **6**, 92% and 53%, respectively). Both oxidative and



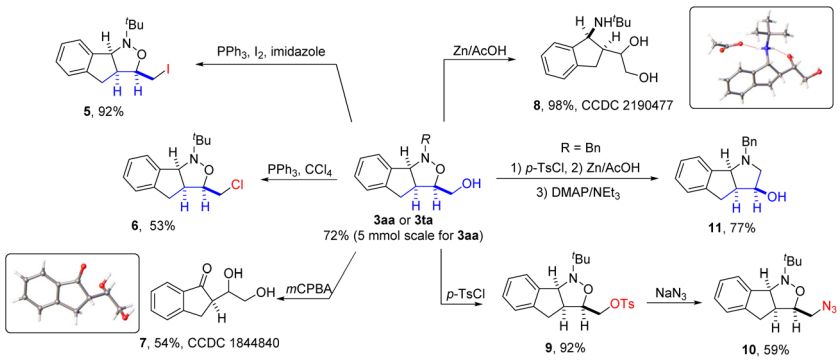
Scheme 2 Scope of nitrones. Reaction conditions: **1** (0.1 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), Ag_2CO_3 (0.05 mmol), PhCl (1 mL), 60 °C, 12 h, under Ar, isolated yield, dr values were determined using ^1H NMR spectroscopy or HPLC, and a single isomer was detected unless noted otherwise.



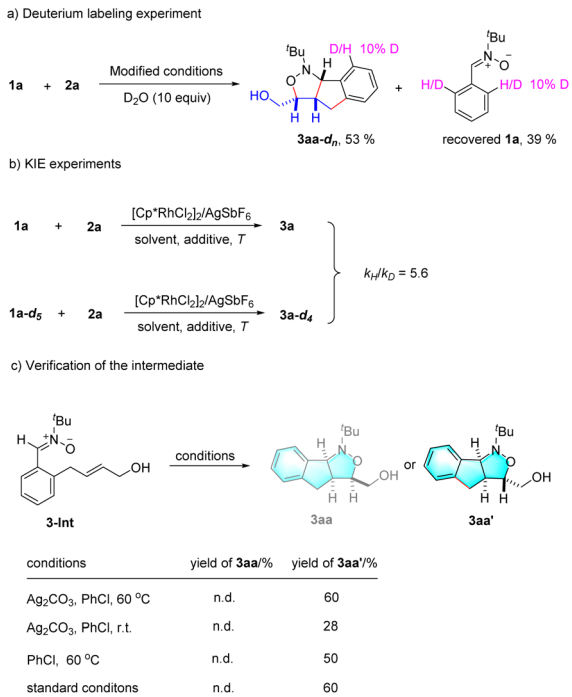
Scheme 3 Scopes of other 1,3-dipoles and dienophiles. [a]**4a** (0.1 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), 4Å MS (60 mg), TFE (1.0 mL), 80 °C, 24 h, under Ar, a single isomer was detected unless noted otherwise. [b]Standard conditions, DCE was used instead of PhCl, 20 h. [c]Standard conditions, NaOAc (0.05 mmol) was added, 12 h. [d]Standard conditions, **2d** (0.3 mmol), 50 °C, 12 h.

reductive ring-openings of **3aa** occurred smoothly to obtain the corresponding ring-opening products (**7** and **8**, 54% and 98%, respectively). The hydroxyl group was converted into an OTs group by performing the reaction with TsCl (**9**, 92%). Subsequent nucleophilic substitution gave the azide product (**10**, 59%). Stepwise treatment of product **3ta** with TsCl, Zn/AcOH and bases generated a hydroindeno[1,2-*b*]pyrrole skeleton (**11**, 77%). Thus, the C–O bonds of the products were shown to be easily converted into C–Cl, C–I or C–N bonds. And the framework can also be transformed to other ring skeletons.

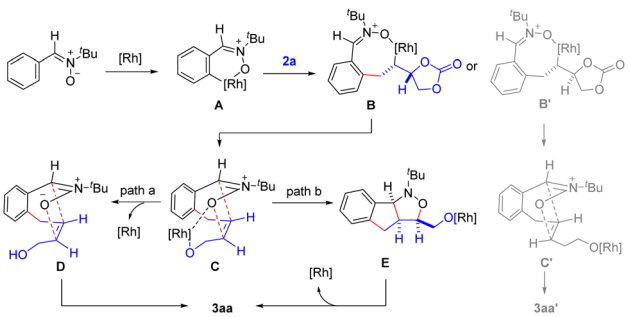
To gain a deeper understanding of the reaction mechanism, some mechanistic experiments were carried out (Scheme 5). A deuterium labeling experiment reaction gave the desired product and recovered starting material with about 10% deuteration at the *ortho*-position of the phenyl ring (Scheme 5a). This result provided evidence for the reversibility of the phenyl C–H activation process. KIE experiments, specifically involving comparing the initial rates of two parallel experiments, gave a KIE value of 5.6, indicating that C–H activation was involved in the rate-determining step (Scheme 5b). Compound **3-Int** containing both a nitrone and *E*-alkene unit was synthesized. However, a different 1,3-DC cycloadduct, namely **3aa'**, was



Scheme 4 Scaled-up synthesis and derivatizations.



Scheme 5 Mechanism studies.



Scheme 6 Proposed mechanism.

detected with moderate yield instead of **3aa**.[14] The configuration of **3aa′** was confirmed from the results of ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H TOCSY, NOESY and HRMS experiments. **3-Int** with an *E*-alkene unit was determined from these experiments to not be an intermediate of the reaction (Scheme 5c). Thus, the catalytic system may deliver a different intermediate structure with a *Z*-alkene unit for the construction of the *cis* product. And an auxiliary role of the catalyst also cannot be excluded.

A possible catalytic cycle was proposed according to the above mechanistic experimental results and related literature (Scheme 6).[5,13a,14] According to this proposal, a nitrone-directed C–H activation by the rhodium catalyst gives rhodacycle **A**, which can undergo coordination of and migration insertion into **2a** to afford two possible intermediates, namely **B** or **B′**. Intermediate **B** undergoes stereoselective β-oxygen elimination and decarbonation to give intermediate **C** with the assistance of the chelating coordination of two oxygen atoms. This process installs a *Z*-alkene unit into the molecule, resulting in the final configuration of product **3aa**. Protonation of **C** leads to intermediate **D** and releases the active rhodium catalyst. The subsequent intermolecular *exo*-type 1–3 DC process accesses the desired product **3aa** (path a). The intermolecular *exo*-type 1–3 DC process acting on intermediate **C** with the assistance of the metal center can also lead to the product and the active catalyst (path b). The relatively unstable intermediate **C′**, a species not coordinated with the nitrone moiety, is also expected to be afforded in the path from rhodacycle **B′** to product **3aa′**, but with the instability making this process a minor one. Thus, the single stereoselective product **3aa** is achieved according to the proposed mechanism.

Conclusions

In summary, a simple alkene unit was introduced into each of several nitrone substrates *via* Rh(III)-catalyzed nitrone-directed C–H activation, and further intramolecular *exo*-type 1,3-dipolar cycloadditions yielded the fused *cis* isooxazoline skeleton. The reaction system showed a good substrate scope and excellent regio- and stereo-selectivity levels. It can be applied to realize the late-stage functionalization of some important natural products and pharmaceutical molecules. The derivatizations of

the representative products can be easily performed, leading to diverse transformations.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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