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CHEMOSELECTIVE REDUCTION OF DICARBOXYLIC ACIDS VIA IRIDIUM CATALYZED HYDROSILYLATION

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CHEMOSELECTIVE REDUCTION OF DICARBOXYLIC ACIDS VIA IRIDIUM-CATALYZED HYDROSILYLATION

By

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Abstract

CATALYTIC CHEMO- AND STEREOSELECTIVE HYDROSILYLATION OF DICARBOXYLIC ACID ANHYDRIDES IMIDES

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The University of Texas at Arlington, 2024

Supervising Professor: Junha Jeon

Reduction of esters to aldehydes poses a challenge since the resulting aldehydes are often more reactive than the initial esters toward nucleophilic hydride-reducing agents. Although bulky, more controllable reducing agents such as lithium tri-*tert*-butoxyaluminum hydride or diisobutylaluminum hydride (DIBAL-H) have been developed, they are hazardous, sensitive to moisture and air, needing strict reaction conditions, and unsuitable with a wide range of functional groups. We present the design of an iridium-catalyzed chemoselective hydrosilylation method for dicarboxylic imides, followed by hydrolysis to eliminate the amide and yield aldehydes. This approach offers versatility in general reduction chemistry, holds promise for application in asymmetric synthesis, and facilitates straightforward removal of Evans-type chiral auxiliaries.

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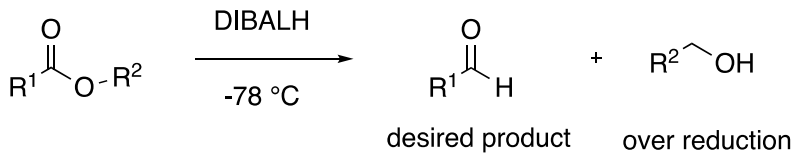
1. Introduction

Aldehydes play diverse and essential roles in biological, chemical, and industrial processes, making them important compounds in numerous fields of science and industry. The significance of aldehydes spans multiple domains. Biologically, they serve as key intermediates in vital metabolic processes like glycolysis and are integral to the synthesis of essential molecules such as amino acids, fatty acids, and vitamins.[1] In the realm of flavor and fragrance, aldehydes like benzaldehyde and vanillin contribute distinct aromas and tastes, defining the characteristic scents of almonds and the flavor of vanilla.[2] Industrially, aldehydes play pivotal roles, with formaldehyde being crucial in the manufacture of resins, adhesives, and textiles, while other aldehydes find applications as solvents, preservatives, and flavor enhancers across diverse industries.[3] In organic synthesis, they serve as crucial intermediates and valuable building blocks for synthesis of complex molecules, engaging in various transformations such as oxidation, reduction, and addition reactions.[4]

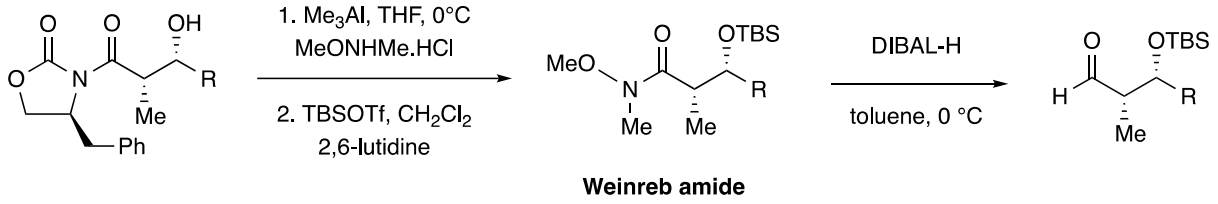
The preparation of aldehydes can be achieved through either reduction of esters and amides or oxidation of primary alcohols. In the course of reduction of esters, the reaction frequently yields over-reduced products, namely alcohols, rather than aldehydes (Scheme 1). This is often due to the higher reactivity of aldehydes towards nucleophilic hydride-reducing agents compared to the starting esters.[5,6,7] To overcome this limitation, large reducing agents such lithium tri-*tert*-butoxyaluminum hydride, or $LiAlH_4$, and diisobutylaluminum hydride (DIBAL-H) have been established.[8,9,10] These chemicals are often hazardous, sensitive to moisture and air, needing strict reaction conditions, and unsuitable with a wide range of functional groups. Furthermore, even with these reagents, substrates are frequently over-reduced. As an alternative, catalytic hydrosilylation followed by silyl group hydrolysis is an option that can reduce carbonyl derivatives.[11,12,13,14]



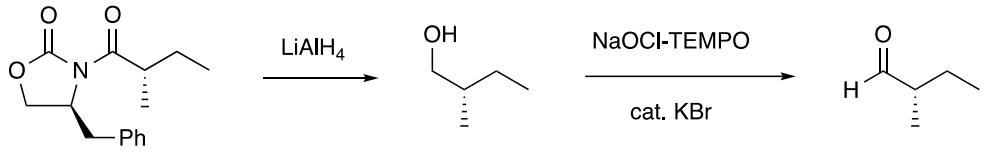
Scheme 1. Reduction of aldehyde using DIBAL-H.

Previous studies have documented the reduction of aldehydes utilizing oxazolidinone auxiliary, wherein the initial formation of the corresponding Weinreb amide is achieved through reaction with (MeO)MeNH. Subsequent treatment with DIBAL-H facilitates the conversion of the amide to the desired aldehyde.[15] Furthermore, the synthesis of (2*S*)-(+)-2-methylbutanal was successfully accomplished in two steps, commencing with exhaustive reaction with LAH, followed by the oxidation of the resulting alcohol.[16,17] Additionally, the controlled reduction of chiral oxazolidinone using DIBAL-H at a lower temperature enabled the direct production of chiral aldehyde, exemplifying the versatility and efficiency of this methodology in accessing enantiomerically enriched compounds(Scheme 2).[18,19,20]

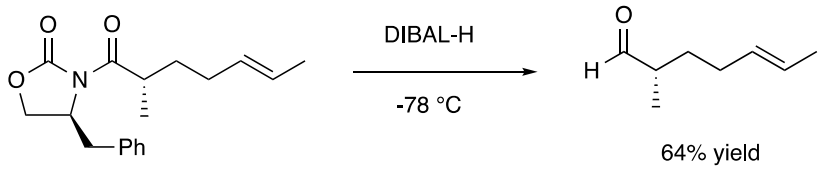
a. Weinreb amide followed by DIBAL-H reduction



b. Exhaustive reduction with LAH followed by oxidation

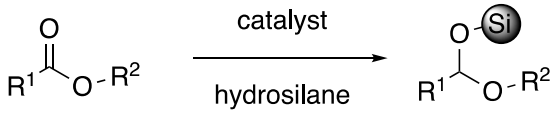


c. Controlled reduction with DIBAL-H



Scheme 2. Processes involving the reduction of Evans oxazolidinones to aldehydes

Transition metal-catalyzed hydrosilylation of aldehydes, ketones, esters, and amides has been a mild and operationally simple reduction method for synthesis of alcohols, aldehydes, enamines, and amines (Scheme 3).[21,22,23] Furthermore, its superior functional group tolerance makes this method widely useful in controlling reduction chemistry.



Scheme 3. Transition metal-catalyzed hydrosilylation of carbonyls

Acetals are chemically equivalent to aldehydes, and upon hydrolysis of acetals aldehydes can be produced. Several acetals such as *O,O*-acetals **1**, O,O-metal acetals **2**, N,O-metal acetals

3, O,O-silyl acetals **4**, N,O-silyl acetals **5** can function as aldehyde equivalents (Figure 1). However, there are a very few methods to reduce esters to silyl acetals in a controlled manner.[24]

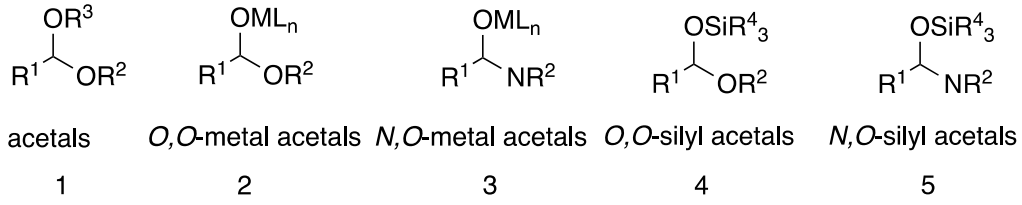
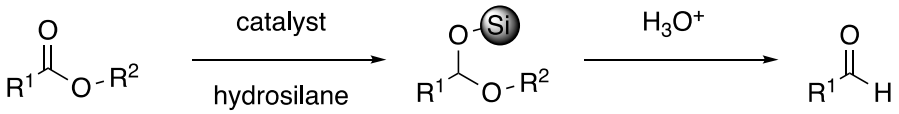


Figure 1. Various acetals.

While expensive platinum-based catalysis is most popular in hydrosilylation chemistry, particularly the silicone sector which requires almost all of the world's platinum consumption[25,26,27,28] hydrosilylation of esters and amides requires less expensive rhodium, iridium, and ruthenium catalysts. Among others, Brookhart developed one of the most effective methods for hydrosilylation of esters and secondary amide with dihydrosilanes and the binuclear iridium complex $[Ir(coe)_2Cl]_2$ as a precatalyst(Scheme 4).[29,30] This process provides silyl acetals, leading to aldehydes, and secondary amines, respectively under mild reaction conditions.[31,32,33,34,

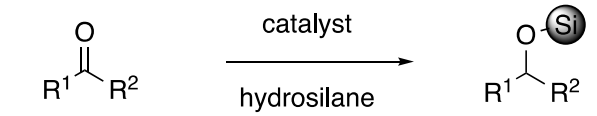


Scheme 4. Reduction of ester through catalytic hydrosilylation

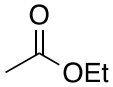
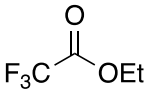
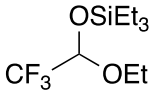
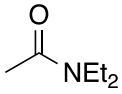
Under the Brookhart conditions, the reactivities of various carbonyl compounds, such as ketones, esters, and amides, towards Ir-catalyzed hydrosilylation differ significantly (Table 1). In literature, at room temperature, ketones and ethyl acetate undergo carbonyl hydrosilylation quickly to achieve quantitative conversions in 0.3 h (Table 1, entries 1 and 2). Notably, when an electron-withdrawing group is introduced into the ester, a corresponding silyl acetal was selectively formed

by a single hydrosilylation, even with use of excess silane (entry 3). The acetal generated by first hydrosilylation has less basicity, and the silyl acetal has less inclination to ionize, which is probably why single hydrosilylation is preferred. *N*,*N*-diethyl acetamide undergoes hydrosilylation (42% conversion) to provide Et_3N and disiloxane (entry 4). There is no longer any evidence of amide intake after 16 hours. The product Et_3N generated during the reaction may deactivate the electrophilic, catalytically active Ir species, causing hindrance of hydrosilylation.[31]

Table 1. General reactivity trend of hydrosilylation of various carbonyls

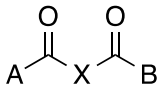


R^1= CH_3, CF_3
R^2= CH_3, OEt

Entry	Substrate	Time (h)	Conversion (%)	Product
1		0.3	quantitative	
2		0.3	quantitative	$EtOSiEt_3$ (70%) + Et_2O (30%)
3		22	95	
4		16	42	NEt_3 + Et_3Si-O-$SiEt_3$

2. Research design for chemoselective reduction of dicarboxylic acids via Ir-catalyzed hydrosilylation.

Despite the success of hydrosilylation of various carbonyls, this chemistry has not been well studied in structurally complex molecular settings. The objective of my research is to develop catalytic chemoselective Ir-catalyzed hydrosilylation of dicarboxylic imides and establish the fundamental reactivity patterns (Figure 2). The hypothesis for this research is that iridium catalyst with dihydrosilanes to form a binuclear silylene-bridged iridium dimer enables controlled carbonyl hydrosilylation, differentiating between two carbonyls holding different sterics and electronics within 1,3-dicarbonyls. This process provides carbonyl hydrosilyl acetals, ultimately leading to aldehydes upon acidic workup.



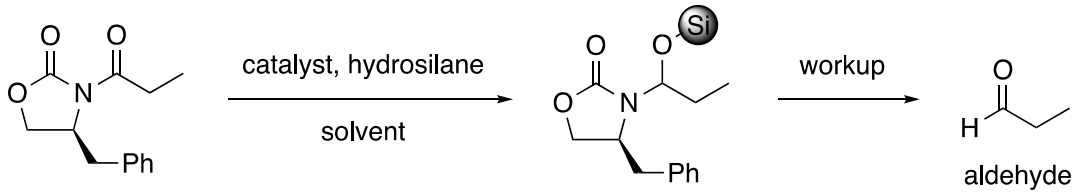
X= O, N, S

Figure 2. Dicarboxylic acid compound

Evans oxazolidinone auxiliary-based asymmetric synthesis is one of the most versatile and powerful strategies for the enantioselective construction of architecturally complex molecules. This method uses temporary, chiral oxazolidinone auxiliaries which serve as a chiral template, dictating the stereochemical fidelity of subsequent synthetic transformations. The Evans oxazolidinone auxiliary has been extensively utilized in various asymmetric transformations, such as asymmetric aldol reactions, Michael additions, Mannich reactions, and Diels-Alder reactions, among several others. Upon completion of the asymmetric transformations, the oxazolidinone auxiliary can be removed via hydrolysis, oxidative cleavage, reductive cleavage, and nucleophilic substitution. In reductive cleavage methods, lithium aluminum hydride ($LiAlH_4$) or

diisobutylaluminium hydride (DIBAL-H) are commonly employed, especially when substrates are sensitive to acidic or basic conditions. However, previously developed aluminum-based reducing agents have achieved only partial success, as Evans oxazolidinone substrates are often directly reduced to alcohols. This occurs because the resulting aldehyde intermediates exhibit higher reactivity toward the reducing agents compared to the starting materials. This requires additional redox adjustments to prepare the corresponding aldehydes for the subsequent transformations.

To address this issue, we aimed to examine this operationally simple, controlled Ir-catalyzed reductive transformation in the Evans oxazolidinone auxiliary system (Scheme 5). To the best of our knowledge, Ir-catalyzed hydrosilylation of the Evans oxazolidinone auxiliary system to produce *N*,*O*-silyl acetal has not been reported. Our Ir-catalyzed hydrosilylation method presents a more step-economical approach to reductive transformations of the Evans oxazolidinone auxiliary system, allowing for the direct formation of aldehydes. This minimizes the need for excessive redox adjustments in the synthesis process. A notable feature of this reaction is to introduce a new chiral center to the substrates, and the diastereoselectivity needs to be recorded. Upon completion of the reaction, the chiral auxiliary is removed, which can be recovered.



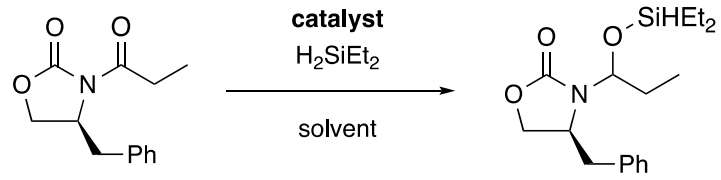
Scheme 5. Reduction of the Evans oxazolidinone auxiliary system to aldehyde via Ir-catalyzed hydrosilylation

3.Initial studies

3a. Chemoselectivity study

Since several group 8 and 9 metal complexes are known to catalyze addition of hydrosilanes across C=O double bonds,[22,23,24] we first investigated the catalytic reactivity of iridium catalyst such as $[Ir(coe)_2Cl]_2$ (coe = cyclooctene) and $[Ir(cod)OMe]_2$ (cod = cyclooctadiene) for chemoselective hydrosilylation of (*S*)-4-benzyl-3-propionyloxazolidin-2-one (Scheme 7, Table 2). In fact, both iridium catalysts, $[Ir(coe)_2Cl]_2$ and $[Ir(cod)OMe]_2$. Following a comprehensive investigation of iridium catalysts along with various reaction parameters including solvents (e.g., THF and DCM) and temperature, amide carbonyl exclusively underwent hydrosilylation over carbarmate carbonyl, leading to *N,O*-silyl acetals, where we did not observe hydrosilylation of carbarmate. Further optimization studies revealed that the more electron-rich $[Ir(cod)OMe]_2$ (cf., $[Ir(coe)_2Cl]_2$), in combination with the less coordinating solvent DCM, afforded the *N,O*-silyl acetal product in nearly quantitative yield and exhibited significantly faster kinetics (3 h vs. 12 h) (Table 2). This reduction protocol using chemoselective hydrosilylation of dicarboxylic acid amide required 1 mol% of iridium catalyst and excess silane (Et_2SiH_2, 3 equiv), possibly due to its volatility. In addition, the chemoselective hydrosilylation exhibited a high diastereoselectivity (>20:1 *dr*), where the absolute stereochemistry of the newly generated chiral center was not determined yet (Table 2, entry 9).

Table 2. Chemoselective hydrosilylation and reaction optimization.



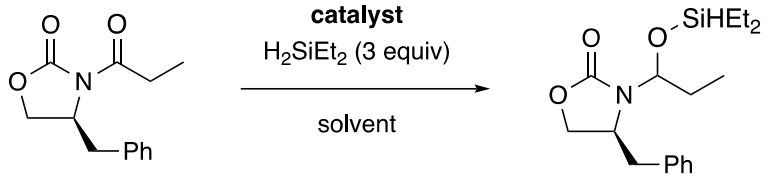
Entry	Catalyst (1 mol %)	Equivalents of H_2SiEt_2	Solvent (1 M)	Temperature (°C)	Time (h)	Yield (%)[a]
1	$[Ir(coe)_2Cl]_2$	3	THF (3 M)	rt	24	42
2	$[Ir(coe)_2Cl]_2$	3	THF (3 M)	40	24	31
3	$[Ir(coe)_2Cl]_2$	3	THF	rt	6	52
4	$[Ir(coe)_2Cl]_2$	3	THF	40	2	54
5	$[Ir(coe)_2Cl]_2$	3	DCM	rt	2	65
6	$[Ir(coe)_2Cl]_2$	3	DCM	40	2	55
7	$[Ir(cod)OMe]_2$	3	THF	rt	36	67
8	$[Ir(cod)OMe]_2$	3	THF	40	3	39
9	$[Ir(cod)OMe]_2$	3	DCM	rt	4	80

[a]NMR yield in C_6D_6 using 1,3,5-trimethoxybenzene (TMB) as internal standard.

3b. Catalyst loading

Optimization of catalyst loading and solvent selection was conducted, with tetrahydrofuran (THF) and dichloromethane (DCM) being investigated as potential solvents (Table 3). The results indicated that employing THF as the solvent with $[Ir(coe)_2Cl]_2$ and $[Ir(cod)OMe]_2$ catalysts yielded moderate yields across a range of catalyst loadings from 0.2 to 2 mol% (Table 3, entries 1, 2, 6, 7). Conversely, utilizing DCM as the solvent in conjunction with $[Ir(cod)OMe]_2$ catalyst resulted in good yields with catalyst loadings ranging from 0.2 to 2 mol% (Table 3, entries 3, 4, 5). These findings underscore the importance of solvent choice in optimizing catalytic performance and highlight the suitability of DCM for achieving high yields in the studied reaction system.

Table 3. Optimization of catalyst loading.



Entry	Catalyst (mol %)	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	$[Ir(cod)OMe]_2$ (0.2)	THF	40	6	58
2	$[Ir(cod)OMe]_2$ (1)	THF	rt	3	66
3	$[Ir(cod)OMe]_2$ (0.2)	DCM	40	2	91
4	$[Ir(cod)OMe]_2$ (0.5)	DCM	40	20 min	88
5	$[Ir(cod)OMe]_2$ (1)	DCM	40	40 min	97
6	$[Ir(coe)_2Cl]_2$ (2)	THF	rt	6	52
7	$[Ir(cod)OMe]_2$ (2)	THF	rt	1	57

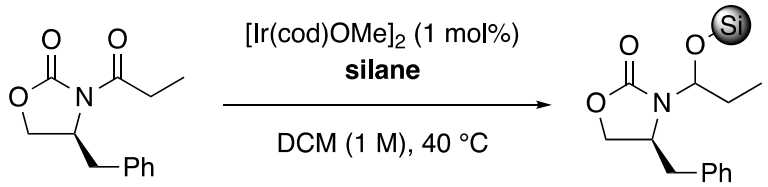
[a]NMR yield in C_6D_6 using 1,3,5-trimethoxybenzene (TMB) as internal standard.

3c. Hydrosilylation of various silanes

We next studied the impact of hydrosilanes on hydrosilylation of (*S*)-4-benzyl-3-propionyloxazolidin-2-one (Table 4). In this study, the reaction was carried out using C_6D_6 as solvent at 40 °C. Monohydrosilane did not produce the desired *N,O*-acetal (Table 4, entry 1). Dihydrosilanes proved to be most effective, where H_2SiEt_2 gave the product in 97% yield in 40 min and $H_2SiPhMe$ afforded the product in 57% yield in 4 h (Table 4, entry 4 and 5). Other silanes including siloxanes and trihydrosilane were ineffective (Table 4, entry 2, 3, and 6). The result

suggests that dihydrosilanes can produce catalytically active, binuclear silylene-bridged iridium dimer most effectively with iridium precatalyst.

Table 4. Scope of silanes.

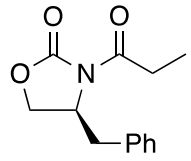


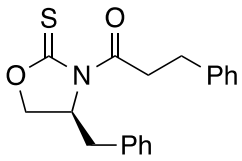
Entry	Silane (3 equiv)	Time (h)	Yield (%)[a]
1	$HSiEt_3$	4	0
2	PHMS	4	2
3	TMDS	4	3
4	H_2SiEt_2	40 min	97
5	$H_2SiPhMe$	4h	57
6	H_3SiPh	4h	2

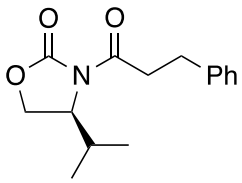
[a]NMR yield in C_6D_6 using 1,3,5-trimethoxybenzene (TMB) as internal standard

4. Scope studies

To demonstrate the synthetic utility of this newly developed method, we studies several Evans and Crimmins chiral auxiliaries to study the chemoselective hydrosilylation (Figure 3). Benzyl and isopropyl-substituted Evans chiral auxiliaries underwent hydrosilylation in excellent yields (97% and 91%) in 40 min. Hydrosilylation of Crimmins chiral auxiliaries took a long reaction time (12 h) and slightly diminished yield (85%).





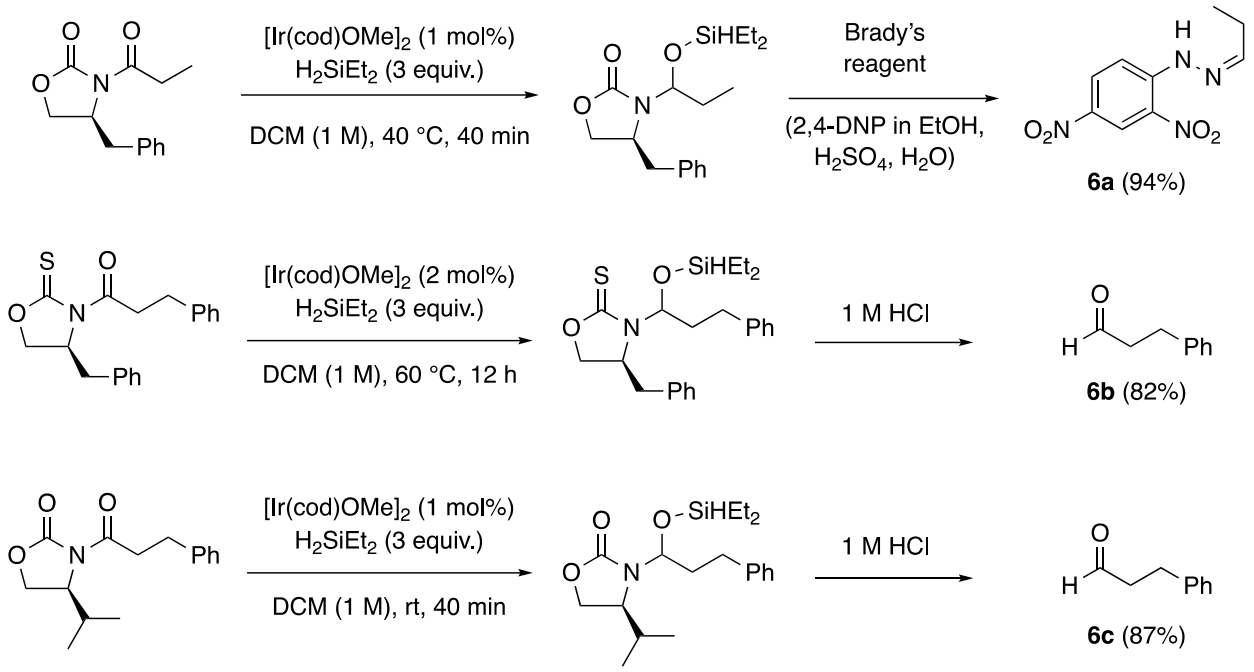


	4a	**4b**	**4c**
catalyst:	1 mol%	2 mol%	1 mol%
Temperature:	40 °C	60 °C	rt
time:	40 min	12h	40 min
yield:	97%	85%	91%

Figure 3. Chemoselective hydrosilylation of Evans and Crimmins chiral auxiliaries

5. Isolation of aldehydes

Upon the success with chemoselective hydrosilylation, we studied the isolation of the corresponding aldehydes (Scheme 6). Aldehyde having low molecular weight was converted to the corresponding hydrazone using Brady's reagent. For instance, propanal was converted to the corresponding hydrazone and the solid precipitate was isolated in 94% yield (**6a**). Other aldehydes were isolated through flash column chromatography, after acidic workup of *N,O*-silyl acetals. In this case, hydrocinnamaldehyde from Evans and Crimmins chiral auxiliaries was obtained in 82% and 87% yield, respectively (**6b** and **6c**).



Scheme 6. Isolation of aldehydes from hydrosilylation

6. Future scope

Encouraged by the promising initial result, we aim to systematically investigate the scope of this reaction. Various dicarboxylic imides will be evaluated to examine the chemoselective hydrosilylation reactions (Figure 4). This study includes α, β, and γ-substituted chiral substrates (**4a-c**). Additionally, we will explore the hydrosilylation of Evans chiral auxiliaries containing alkene and alkyne functionalities (**4d** and **4e**) to assess the compatibility of carbonyl hydrosilylation with alkene/alkyne hydrosilylation.

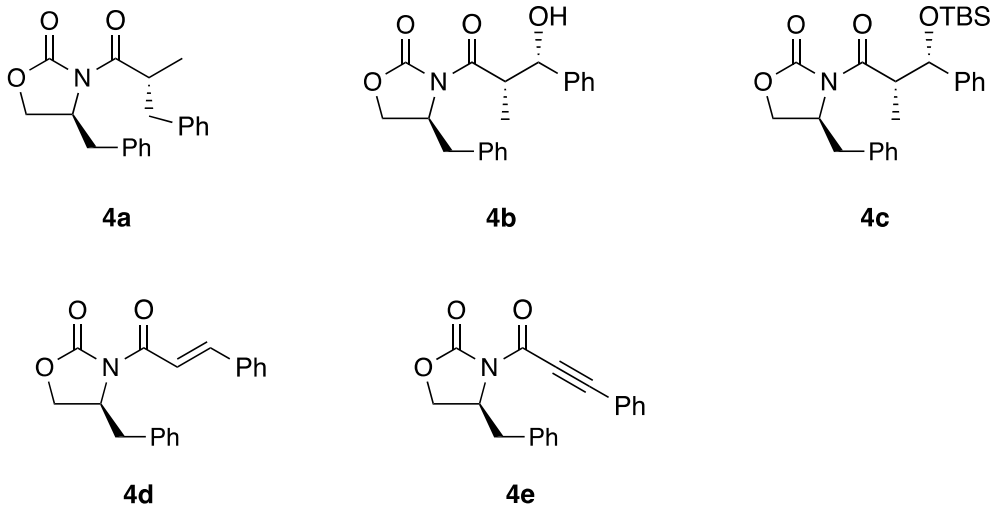


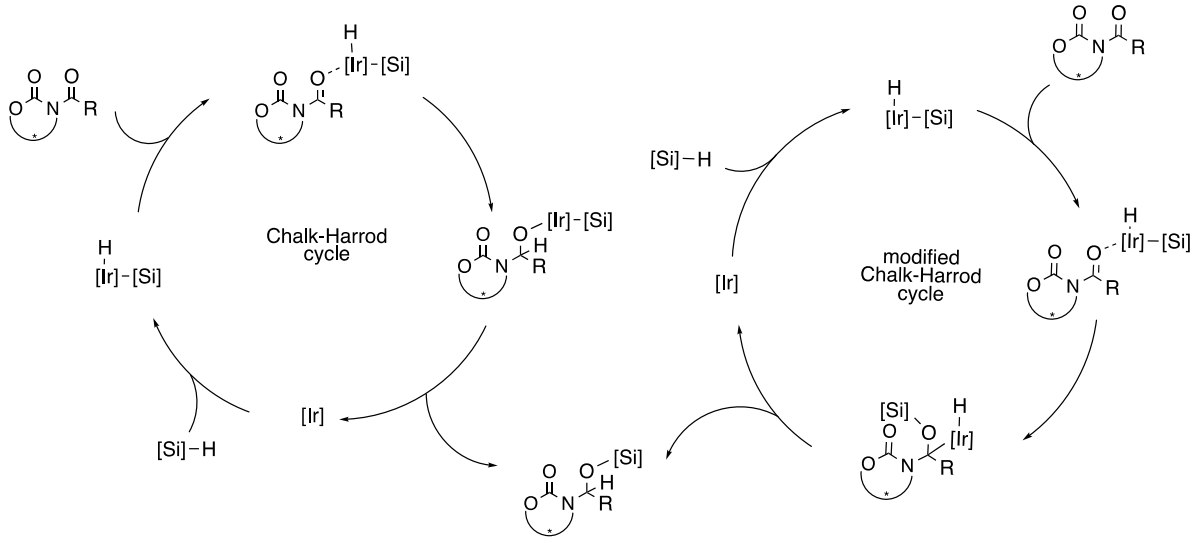
Figure 4. Future scopes studies

7. Proposed mechanism

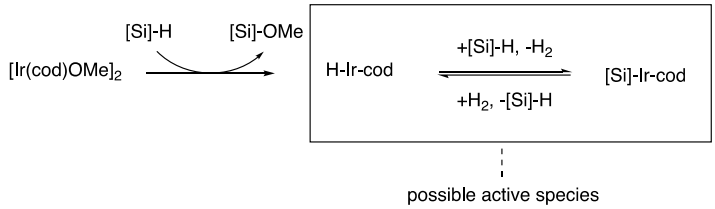
There are two widely accepted mechanisms for transition metal-catalyzed hydrosilylation. The first mechanism, known as the Chalk–Harrod mechanism, proceeds through elementary steps including oxidative addition of a Si–H bond to a metal complex, migratory insertion of the carbonyl into the M–H bond, and reductive elimination that regenerates the metal complex (Figure 5A, left). Another proposed mechanism, termed the modified Chalk-Harrod mechanism, suggests oxidative addition of a Si–H bond to a metal complex, migratory insertion of the carbonyl into the M–Si bond followed by C-H reductive elimination (Figure 5A, right).[35] While the nature of the active catalytic species is still under investigation, current understanding suggests that "H-Ir-cod" or "Si-Ir-cod" species are responsible for catalytic activity. H-Ir-cod is formed by the addition of a metal complex with Si-H, eliminating Si-OMe, and upon oxidative addition and reductive elimination of the H-Ir-cod complex produces Si-Ir-cod (Figure 5B 1). It is believed that the oxidative addition of a metal complex in the presence of a Si-H bond leads to the formation of complexes through an intermediate MeO-Ir-cod species via reductive elimination.[36] Other potential explanations, such as generating an electrophilic silyl methoxide by eliminating the active

iridium species after its initial insertion into the Si−H bond, cannot be disregarded. Methodologies like iridium-catalyzed alcohol silylation using a Vaska's compound (Figure 5B 2) suggest similar mechanisms.[37] Additionally, it is proposed that the catalytically active species is a binuclear silylene-bridged iridium dimer, formed by successively replacing the ligands on $[Ir(cod)OMe]_2$, involving cyclooctadiene and methoxide (Scheme B3). X-ray crystallography has previously confirmed that a comparable compound, derived from tBu_2SiH_2, exhibited the bridging silylene structure.[30] In the catalytic cycle, the slowest step appears to be the silylium activation of the carbonyl, involving the transfer of "Et_2HSi^+" to the carbonyl oxygen, yielding Ir-H, which significantly affects reaction rates in substrates deficient in electrons (Table 1, entry 1 vs entry 4). Strong coordinating group substrates slow down the rate of reaction and may necessitate additional catalysts or higher temperatures (Table 1, entry 3). The cycle is completed upon reductive elimination of Ir-H, regenerating the metal complex and allowing the process to be repeated.

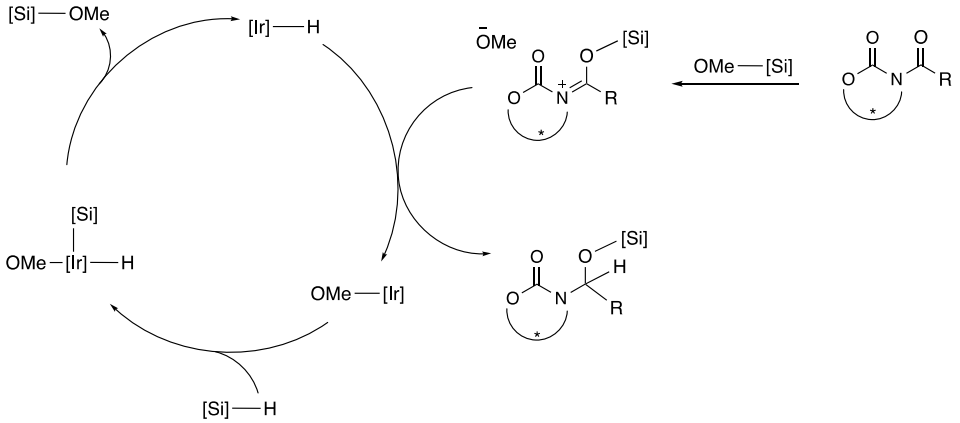
(A) Proposed Chalk-Harrod and Modified Chalk-Harrod Mechanism



(B 1) Proposed generation of active iridium species



(B 2) Proposed mechanism: generation of reactive silyl methoxide



(B 3) Proposed catalytically active species and catalytic cycle

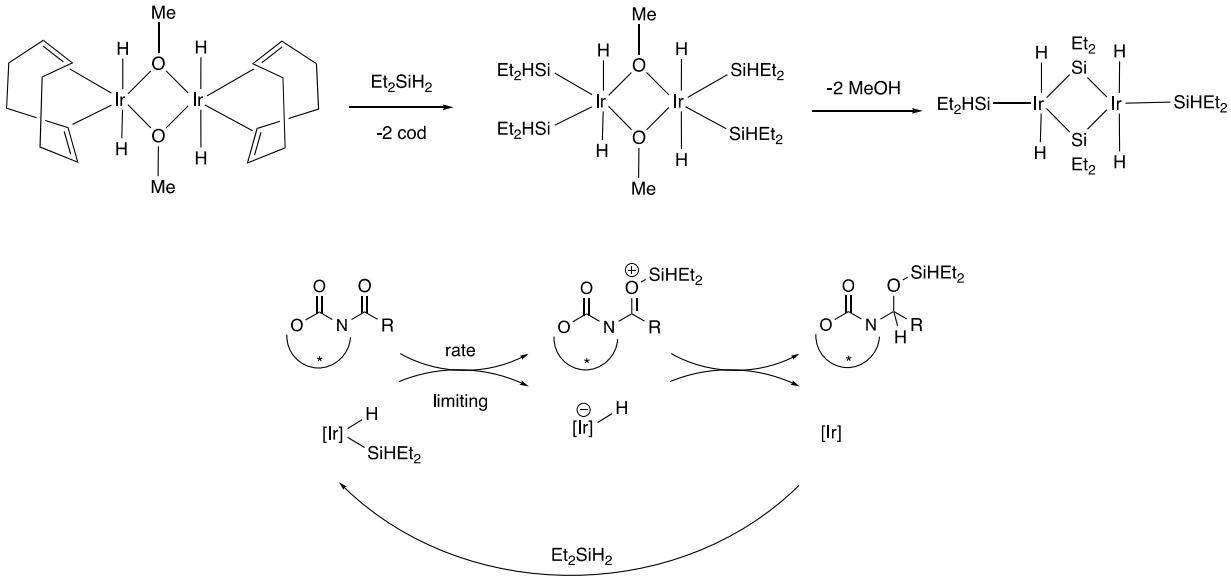


Figure 5 . Current Proposed Mechanisms: (A) Chalk−Harrod and Modified Chalk-Harrod Type Cycles; (B) Proposed active Iridium species; (C) Iridium-Catalyzed Generation of

Reactive Silyl Chloride Species; (D) Proposed catalytically active species and catalytic cycle

8. Summary

Here we have developed a highly efficient method for chemoselective reduction of dicarboxylic acid imides to aldehydes via Ir-catalyzed hydrosilylation. The catalytic system to effect chemoselective hydrosilylation was identified, where electron-rich iridium Ir(cod)OMe]$_2$, dihydrosilane, and less coordinating DCM were required. Acidic workup of the resulting N,O-silyl acetals or hydrazone forming reaction directly provided the corresponding aldehydes. We will further evaluate the scope and functional group tolerance of this method. Finally, this method offers a more step-economical approach to reductive transformations of the Evans and Crimmins-type oxazolidinone auxiliary system, minimizing excessive redox adjustments.

Appendix A: List of Abbreviations

δ: chemical shift (ppm)

mL: milliliter

μm: micrometer

Ac: acetate

Bn: benzyl

nBuLi: n-butyl lithium

C: Celsius

calcd: calculated

cat.: catalyst, catalytic amount

coe: cyclooctene

COD: 1,5-cyclooctadiene

Cy: cyclohexyl

DIBALH: diisobutylaluminum hydride

PHMS: Polymethylhydrosiloxane

TMDS: 1,1,3,3-Tetramethyldisiloxane

DCM: dichloromethane

THF: tetrahydrofuran

equiv.: equivalent

Et: ethyl

g: gram

h: hours

min: minute

t: time

T: temperature

HRMS: high resolution mass spectrometry

Hz: hertz

GC-MS: Gas chromatography-mass spectrometry

IR: infrared spectroscopy

J: coupling constant, NMR spectroscopy

M: molar

[M+]: molecular ion

Me: methyl

min: minutes

mg: milligram

MHz: megahertz

mL: milliliter

mmol: millimole

MW: molecular weight

Ph: phenyl

NMR: nuclear magnetic resonance spectroscopy

HPLC: High performance liquid chromatography

TOF: Time of flight

APCI: Atmospheric pressure chemical ionization

MPLC: Medium pressure liquid chromatography

$NaSO_4$: Sodium sulphate

NH_4Cl: Ammonium chloride

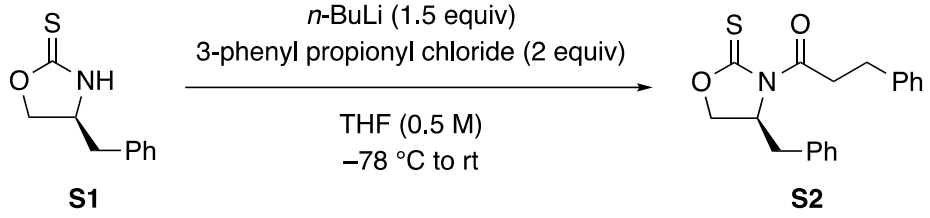
Å: Angstrom

Appendix B: Experimental Procedures

Materials and Method

Reactions which required anhydrous conditions were undergoing the nitrogen environment in flame-dried glassware. Anhydrous dichloromethane (DCM) was distilled from CaH_2. Anhydrous tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone. All reagents and other solvents which purchased from the commercial were used as supplied. ^1H, ^2H, and ^{13}C NMR spectra were recorded on JEOL Eclipse Plus 500 (500 MHz) and JEOL ECX 300 (300 MHz) spectrometers. NMR spectra were recorded by 400 or 500 MHz NMR spectrometer. ^1H NMR chemical shifts are referenced to chloroform-D (7.26 ppm) and benzene-D_6 (7.16 ppm). ^{13}C NMR chemical shifts are referenced to $^{13}CDCl_3$ (77.23 ppm), and benzene-D_6 (128.39ppm). The following abbreviations are used to describe multiplets: s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), m (multiplet), nfom (non-first- order multiplet), and br (broad). ^1H NMR assignments are indicated by structure environment (e.g., CH_aH_b). Infrared (IR) spectra were recorded using neat (for liquid compound) from a concentrated DCM solution. Absorptions are reported in $cm^{-1.}$ Only the most intense and diagnostic peaks are reported. High-resolution mass spectra (HRMS) were recorded in atmospheric-pressure chemical ionization and time-of-flight (APCI/TOF) mode. Samples were introduced as solutions in DCM solution. MPLC refers to medium pressure liquid chromatography (25-200 psi) using hand-packed columns of silica gel (20-45 μm, spherical, 70 Å pore size) with a HPLC pump and a differential refractive index detector. TLC analysis experiments were performed on F254 plate and stained by potassium permanganate solution.

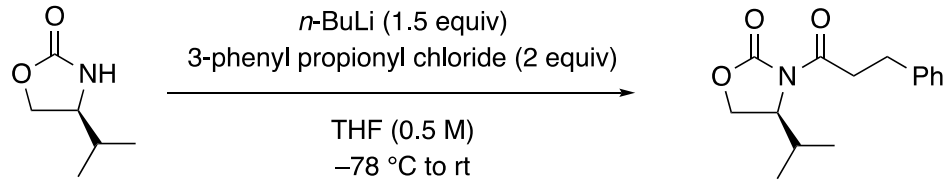
Procedure for preparation of (*S*)-1-(4-benzyl-2-thioxooxazolidin-3-yl)-3-phenylpropan-1-one



S1 **S2**

n-BuLi (4.3 mL, 1.5 equiv, 6 mmol, 1.4 M in hexane) was added dropwise to a solution of (*S*)-4-benzyloxazolidine-2-thione **S1** (773 mg, 4 mmol) in THF (8 mL, 0.5 M) at –78 °C. The mixture was stirred for 15 min at –78 °C, following which 3-phenyl propionyl chloride (1.18 mL, 8 mmol) was added. The resulting mixture was stirred at –78 °C for 30 min and warmed to room temperature. After being stirred for 2 h, the mixture was quenched by the addition of aqueous saturated NH_4Cl. The layers were separated, and the organic layer was extracted three times with DCM and washed with brine. The organic phase was then dried over anhydrous $NaSO_4$, filtered with a filter paper, and concentrated under reduced pressure. The crude material was subsequently purified through flash chromatography (hexanes: EtOAc = 5:1) to yield a sticky liquid product **S2** (1042 mg, 80% yield).

Procedure for preparation of (*S*)-4-isopropyl-3-(3-phenylpropanoyl)oxazolidin-2-on

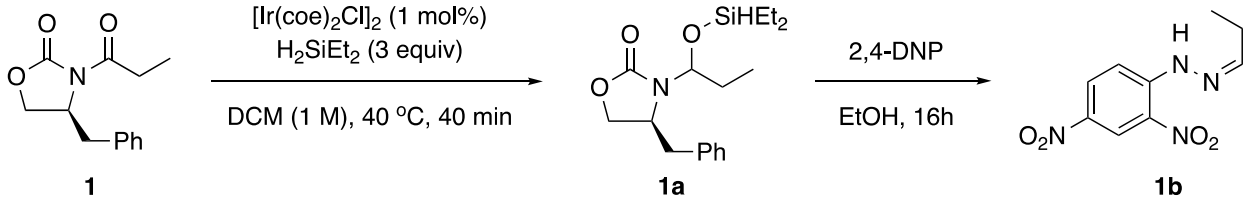


S3 **S4**

n-BuLi (4.3 mL, 1.5 equiv, 6 mmol, 1.4 M in hexane) was added dropwise to a solution of (*S*)-4-isopropyloxazolidin-2-one **S3** (517 mg, 4 mmol) in THF (8 mL, 0.5 M) at –78 °C. The mixture

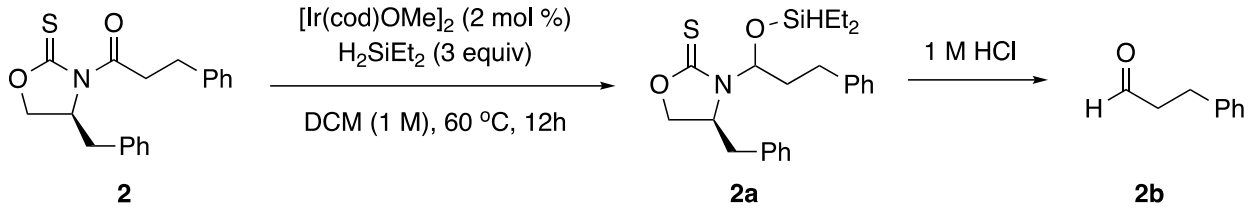
was stirred for 15 min at –78 °C, following which 3-phenyl propionyl chloride (1.2 mL, 8 mmol) was added. The resulting mixture was stirred at –78 °C for 30 min, and warmed to room temperature. After being stirred for 2 h, the reaction mixture was quenched by the addition of aqueous saturated NH_4Cl. The layers were separated, and the organic layer was extracted three times with ethyl acetate and washed with brine. The organic phase was then dried over anhydrous $NaSO_4$, filtered with a filter paper, and concentrated under reduced pressure. This crude material was subsequently purified through flash chromatography (Hexanes: EtOAc = 10:1) to yield white solid product **S4** (730 mg, 70% yield).

Procedure for reduction of Evans oxazolidine to aldehyde via Ir-catalyzed hydrosilylation



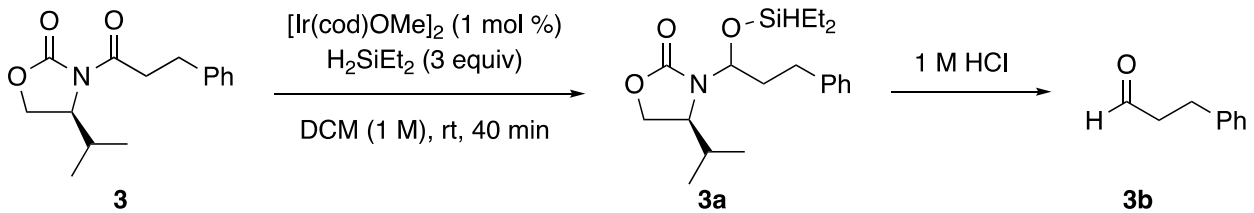
$[Ir(cod)OMe]_2$ (3 mg, 1 mol%), oxazolidinone **1** (93 mg, 0.4 mmol), and DCM (0.4 ml, 1 M) were added to a flame-dried flask. Diethylsilane (0.16 mL, 1.2 mmol) was then added to the mixture. The septum on the vial was replaced by a screw cap with a Teflon liner. The reaction mixture was warmed to 40 °C and stirred for 40 min. Once the hydrosilylation is completed, the reaction mixture was dissolved in ethanol (3 mL) and Brady's reagent [prepared by mixing 2,4-DNP (120 mg), H_2SO_4 (0.4 mL), H_2O (0.6 mL), EtOH (2 mL)] was added dropwise. The reaction mixture was stirring for 16h, during which precipitates formed. The liquid was decanted, and the precipitates were washed three times with pentane. Volatiles were removed under reduced pressure, producing the hydrazone product as an orange solid (225 mg, 94% yield).

Procedure for reduction of Crimmins oxazolidine-2-thione to aldehyde via Ir-catalyzed hydrosilylation



$[Ir(cod)OMe]_2$ (5.3 mg, 2 mol%), oxazolidine-2-thione **2** (130.2 mg,1 equiv, 0.4 mmol), and DCM (0.4 ml, 1 M) were added to a flame-dried flask. Diethylsilane (0.16 mL, 3 equiv, 1.2 mmol) was added to the mixture. The septum on the vial was replaced by a screw cap with a Teflon liner. The reaction mixture was warmed to 60 ˚C and heated for 12 h. After the hydrosilylation is completed, the resulting silyl acetal was hydrolyzed under acidic conditions (1M HCl) by stirred for 30 min. The layers were separated, and the organic layer was extracted three times with DCM and washed with brine. The organic phase was then dried over anhydrous $NaSO_4$, filtered with a filter paper, and concentrated under reduced pressure. The organic layer was separated with DCM, dried with $NaSO_4$, rotor vap and dried under vacuum. The crude product was subsequently purified through column chromatography (Hexane/EtOAc in 10:1), producing the corresponding aldehyde (44 mg, 82% yield).

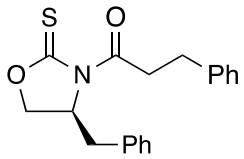
Procedure for reduction of Evans oxazolidine_4-isopropyl to aldehyde via Ir-catalyzed hydrosilylation



[Ir(cod)OMe]$_2$ (2.65 mg, 1 mol%), oxazolidine-4-isopropyl **3** (104.55 mg,1 equiv, 0.4 mmol), and DCM (0.4 ml, 1 M) were added to a flame-dried flask. Diethylsilane (0.16 mL, 3 equiv, 1.2 mmol) was added to the mixture. The septum on the vial was replaced by a screw cap with a Teflon liner. The reaction mixture was stirred at room temperature for 40 minutes. After the hydrosilylation is completed, the resulting silyl acetal was hydrolyzed under acidic conditions (1M HCl) by stirred for 30 min. The layers were separated, and the organic layer was extracted three times with ethyl acetate and washed with brine. The organic phase was then dried over anhydrous $NaSO_4$, filtered with a filter paper, and concentrated under reduced pressure. The organic layer was separated with DCM, dried with $NaSO_4$, rotor vap and dried under vacuum. The crude product was subsequently purified through column chromatography (Hexane/EtOAc in 10:1), producing the corresponding aldehyde (47 mg, 87% yield).

Appendix C: Spectral data of the compounds

(*S*)-4-Isopropyl-3-(3-phenylpropanoyl)oxazolidin-2-one (S2)



Yield: 531 mg, 82%.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.17 [m, 10H, Ar*H*], 5.30 (CH_2Cl_2), 4.95-4.89 [dddd, *J* = 10.8, 5.8, 3.2, 3.2 Hz, 1H, NC*H*Bn], 4.31 [dd, *J* = 9.3, 2.4 Hz, 1H, OCH_aH_b], 4.26 [dd, *J* = 9.3, 7.5 Hz, 1H, OH$_a$*H*$_b$], 3.74 [ddd, *J* = 15.1, 8.8, 6.1 Hz, 1H, C=OC$H_aH_bCH_2$Ph], 3.60 [ddd, *J* = 15.4, 8.6, 6.6 Hz, 1H, C=OCH$_a$*H*$_b$CH$_2$Ph], 3.26 [dd, *J* = 13.3, 3.4 Hz, 1H, NCHCH_aH_bPh], 3.09 [ddd, *J* = 14.4, 8.7, 6.2 Hz, 1H, CH$_2$CH_aH_bPh], 3.03 [ddd, *J* = 14.4, 8.7, 6.7 Hz, 1H, CH$_2$CH$_a$*H*$_b$Ph], and 2.76 [dd, *J* = 13.3, 10 Hz, 1H, NCHCH$_a$*H*$_b$Ar].

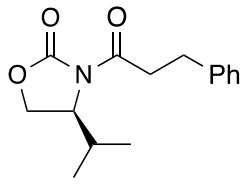
^{13}C NMR ($CDCl_3$, 125 MHz): δ 185.4, 173.3, 140.5, 135.3, 129.6, 129.1 128.67, 128.65, 127.5, 126.4, 70.5, 60.1, 39.1, 37.7, and 30.6.

IR (neat): 3025 (w), 2923 (w), 1686 (s), 1349 (s), 1326 (s) cm^{-1}.

TLC: R_f = 0.4 in 10:1 hexanes:EtOAc.

HRMS (**APCI/TOF**): Calcd for $(M+H)^+$ $(C_{19}H_{20}NO_2S)^+$: 326.1214. Found: 326.1195.

(*S*)-4-Isopropyl-3-(3-phenylpropanoyl)oxazolidin-2-one (S4)



Yield: 732 mg, 70%

^{1}H NMR ($CDCl_3$, 500 MHz): 7.29-7.22 [m, 4H, Ar*H*], 7.18 [t, *J* = 7.1 Hz, 1H, Ar*H*], 4.42-4.36 [ddd, *J* = 7.6, 7.6, 3.7 Hz, 1H, NC*H*CH], 4.23-4.14 [nfom, 2H, OCH_2], 3.24-3.28 [ddd, *J* = 15.3, 8.6, 6.1 Hz, 1H, C=OCH_aH$_b$CH$_2$Ph], 3.24-3.16 [ddd, *J* = 15.5, 8.7, 7.2 Hz, 1H, C=OCH$_a$$H_bCH_2$Ph], 3.00 [ddd, *J* = 14.0, 8.4, 6.7 Hz, 1H, CH$_2$CH_aH$_b$Ph], 2.97 [ddd, *J* = 14.0, 8.5, 7.0 Hz, 1H, CH$_2$CH$_a$$H_b$Ph], 2.33 [doublet of septets, *J* = 7.1, 7.1 Hz, 1H, C*H*(CH$_3$)$_2$], 0.88 [d, *J* = 7.1 Hz, 3H, CH(CH_3)$_2$], and 0.81 [d, *J* = 7.1 Hz, 3H, CH(CH_3)$_2$].

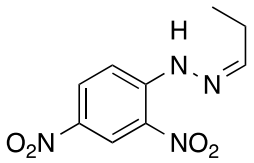
^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.4, 154.2, 140.6, 128.6, 128.5, 126.3, 63.5, 58.5, 37.2, 30.5, 28.4, 18.0, and 14.7.

IR (neat): 3060 (w), 2954 (w), 1771 (br), 1702 (s), and 1453 (m) cm^{-1}.

TLC: R_f = 0.3 in 20:1 hexanes:EtOAc.

HRMS (**APCI/TOF**): Calcd for $(C_{15}H_{20}NO_3)^+$: 262.1443. Found: 262.1412.

(*Z*)-1-(2,4-Dinitrophenyl)-2-propylidenehydrazine (1b)



Yield: 223 mg, 94%

^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.3 [br s, 1H, N*H*], 8.84 [d, *J* = 2.7 Hz, 1H, (NO_2)CC*H*C(NO_2)], 8.30 [dd, *J* = 9.7, 2.7 Hz, 1H, C*H*C(NO_2)CHC(NO_2)], 7.99 [t, *J* = 4.8 Hz, 1H, N=C*H*], 7.83 [d, *J* = 9.7 Hz, 1H, CHC*H*CNH], 2.33 [qd, *J* = 7.5, 4.8 Hz, 2H, CH$_3$CH_2], and 1.07 [t, *J* = 7.4 Hz, 1H, CH$_2$CH_3].

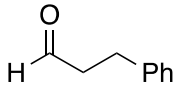
^{13}C NMR ($CDCl_3$,125 MHz): δ 153.5, 145.8, 37.8 130.06, 123.6, 116.6, 100.0, 26.1, and 10.6.

IR (neat): 3292 (br), 3111 (w), 2983 (w), 1612 (m), and 1300 (br) cm^{-1}.

TLC: R_f = 0.5 in 5:1 hexanes: EtOAc.

HRMS (**APCI/TOF**): Calcd for $(C_9H_{11}N_4O_4)^+$: 238.0702. Found: 238.0609.

3-Phenylpropanal (2b & 3b)



Yield: 44 mg, 82% (**2b**) and mg, 47 mg, 87% (**3b**)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.83 [t, *J* = 1.4 Hz, 1H, *H*C=O], 7.32-7.27 [dd, *J* = 7, 7 Hz, 2H, Ar*H*], 7.23-7.19 [m, 3H, Ar*H*], 2.96 [t, *J* = 7.5 Hz, 2H, C*H*$_2$Ph], and 2.79 [td, *J* = 7.0, 1.4 Hz, 2H, O=CHC*H*$_2$].

^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.7, 140.4, 128.7, 128.3, 126.4, 45.4, and 28.2.

IR (neat): 3026 (w), 1720 (s), and 1453 (w) cm^{-1}.

TLC: R_f = 0.4 in 20:1 hexanes:EtOAc.

Reference.: Lozynskyi, A.; Karkhut, A.; Polovkovych, S.; Karpenko, O.; Holota, S.; Gzella, A.K.; Lesyk, R. 3-Phenylpropanal and citral in the multicomponent synthesis of novel thiopyrano[2,3-*d*]thiazoles. *Results in Chemistry* **2022**, 4, 100464.

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