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Displacement of Dinitrogen by Oxygen: A Methodology for the Catalytic Conversion of Diazocarbonyl Compounds to Ketocarbonyl Compounds by 2,6-Dichloropyridine-*N*-oxide

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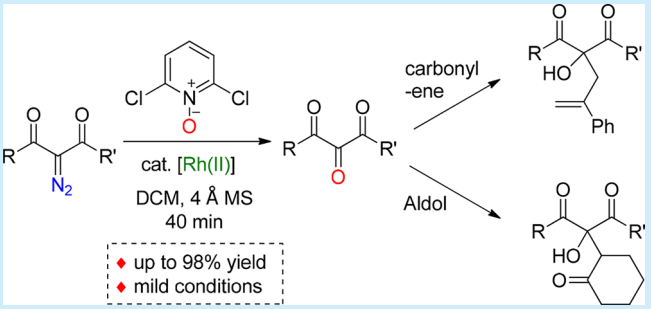
Supporting Information

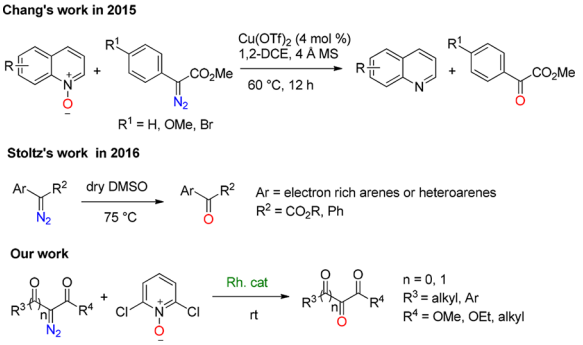
ABSTRACT: Dirhodium(II) catalyzed dinitrogen extrusion from diazocarbonyl compounds by 2,6-dichloropyridine-*N*-oxide forms ketocarbonyl compounds in near-quantitative yields. Reactions occur at room temperature, and the pyridine product does not coordinate with dirhodium(II) to inhibit catalysis. Anhydrous tricarbonyl compounds, as well as dicarbonyl compounds, are conveniently prepared by this methodology, and they have been used in situ for catalytic ene and aldol transformations.



Vicinal tricarbonyl compounds have proven to be versatile synthetic building blocks.[1] The carbon of the middle carbonyl group is highly electrophilic, providing sufficient reactivity for carbon−carbon bond formation with even moderately reactive nucleophiles under mild conditions.[2−5] Access to these vicinal tricarbonyl compounds has been provided by oxidation of 1,3-dicarbonyl compounds,[6] but is most conveniently provided by oxidative conversion of the disubstituted diazomethane formed by diazo transfer to a β-ketocarbonyl compound, typically, but not limited to, β-ketoesters and β-ketoamides.[7] The diazo transfer reaction of β-ketocarbonyl compounds occurs by its well-developed base promoted reaction with organic sulfonyl azides in high yields under mild conditions.[8] The oxidative dinitrogen extrusion step is less well developed, although several methods have been used.[9] One is reaction with dimethyldioxirane (DMDO), formed from acetone and oxone,[10] that when applied to, typically, α-diazo-β-ketoesters can form the anhydrous form of 2,3-diketoesters quantitatively or in high yield; however, since oxone is a somewhat indiscriminate oxidant, DMDO is usually formed separately and then added to the diazo compound. DMDO is commonly used for small-scale reactions.[11] An alternative to DMDO is the use of *tert*-butyl hypochlorite,[12] but with this method the hydrate of the tricarbonyl compound is the product. Since the hydrate significantly reduces the electrophilic reactivity of the vicinal carbonyl compound,[4] alternative methods are sought to allow large-scale production of vicinal tricarbonyl compounds avoiding water or other common nucleophiles that reduce their reactivity.

One approach to the replacement of the dinitrogen of diazo compounds by oxygen has been oxygen atom transfer (Scheme 1). Dimethyl sulfoxide has been recently reported to effect

Scheme 1. Oxygen Transfer Reactions



thermal oxidative dedinitrogenation of aryldiazocarbonyl compounds in good yield, but DMSO was used as the solvent, and the minimum temperature employed was 50 °C for treatment with these normally reactive diazo compounds.[13] Previously, diazoesters had been employed for copper catalyzed oxygen atom abstraction from a variety of *N*-oxides;[14] good to high pyridine yields were obtained for reactions performed at 60 °C with a large excess of the diazo compound. Our interest is in generating a methodology for the construction of vicinal tricarbonyl compounds that could be performed with a mild oxidant under mild conditions avoiding water or other common nucleophiles that would reduce their electrophilic reactivity in subsequent reactions. We now report the efficient generation of anhydrous vicinal di- and tricarbonyl compounds by dirhodium(II) catalyzed reactions between diazocarbonyl

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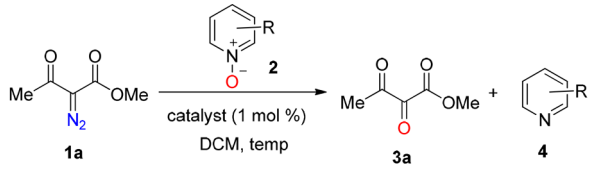
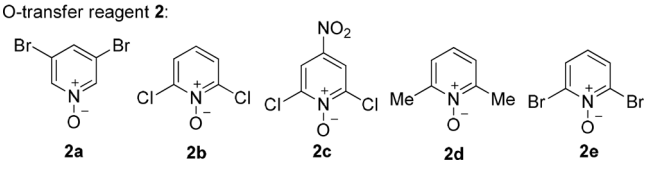
compounds and 2,6-dichloropyridine-*N*-oxide, and their applications for carbon−carbon bond formation.

By recognizing the differences in stabilities of diazocarbonyl compounds (acceptor−acceptor, donor−acceptor, and acceptor),[15] we selected *α*-diazo-*β*-ketoesters as model substrates for dinitrogen replacement by oxygen. These diazo compounds are much more stable than diazoacetates or aryldiazoesters that have been previously employed for this transformation. Their thermal stabilities and resistance to catalytic dinitrogen loss have been described.[9c,16] Treatment of methyl 2-diazo-3-oxobutanoate (methyl diazoacetoacetate, MDAA, **1a**) with either DMSO or pyridine-*N*-oxide resulted in no apparent reaction at room temperature over 24 h, and even in refluxing 1,2-dichloroethane (DCE, 82 °C) this diazo compound exhibited negligible reaction. The addition of rhodium acetate to form an intermediate metal carbene was ineffective with pyridine-*N*-oxide at room temperature, and very slow dinitrogen extrusion was observed at the much higher temperature of refluxing DCE. Since our goal was oxygen transfer that could occur at or below room temperature, we searched for an oxygen transfer reagent that could allow complete reaction to occur within a reasonable time period, and the results of this search are given in Table 1. Pyridine-*N*-oxide and para-substituted pyridine-*N*-oxides (*para*-OMe, −Me, −Cl, NO_2) underwent slow rhodium acetate catalyzed oxygen transfer with MDAA in refluxing DCE but were unreactive at room temperature. In contrast, 2,6-disubstituted pyridine-*N*-oxides underwent smooth oxygen transfer at room temperature with rates of reaction that were dependent on the substituents.

Table 1. Screening Reaction Conditions for 1a[a]



O-transfer reagent **2**:

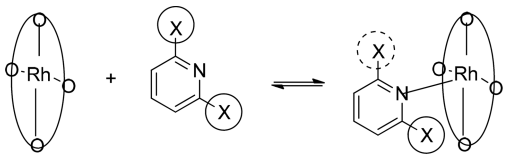


entry	O-transfer reagent	catalyst	temp (°C)	time (h)	yield **3a** (%)[b]
1	**2a**	$Rh_2(OAc)_4$	23	24	0
2	**2b**	$Rh_2(OAc)_4$	23	1	90
3	**2c**	$Rh_2(OAc)_4$	23	1.5	82
4	**2d**	$Rh_2(OAc)_4$	23	24	30
5	**2e**	$Rh_2(OAc)_4$	23	1.5	69
6[c]	**2b**	$Rh_2(oct)_4$	23	0.67	94
7	**2b**	none	23/82	12	0
8	none	$Rh_2(OAc)_4$	23	24	complex

[a]Standard reaction conditions: $Rh_2(OAc)_4$ (2.0×10^{-3} mmol) was added to a 1.0 mL DCM solution of **1a** (0.20 mmol) and pyridine-*N*-oxides **2** (1.0 equiv) at room temperature. [b]NMR yield with 1,3,5-trimethoxylbenzene as internal standard. [c]4 Å Molecular sieves (50 mg) were added into a solution of **1a** (28.4 mg, 0.20 mmol), 2,6-dichloropyridine-*N*-oxide **2b** (32.8 mg, 0.20 mmol, 1.0 equiv) in DCM (1.0 mL). The mixture was stirred for 10 min before the addition of $Rh_2(oct)_4$ (1.56 mg, 2.0×10^{-3} mmol) at room temperature. Reaction time is 40 min.

2,6-Dichloropyridine-*N*-oxide (**2b**) was optimum in its rate of transfer and convenience. However, the oxygen transfer to **1a** using **2b** did not occur with copper(II) triflate[14] at 60 °C over 24 h in DCE, the conditions preciously used by Chang using selected aryldiazoacetates.

The cause for the relative ease of oxygen transfer with 2,6-disubstituted pyridine-*N*-oxides is proposed to be an outcome of weak coordination with the pyridine-*N*-oxide and the structure of rhodium(II) carboxylates whose oxygen ligands provide a barrier to association by its pyridine product (eq 1).



The coordinating ability of pyridine with rhodium(II) carboxylates is very strong,[17] but the electron-rich chloride substituents at the 2- and 6-positions can be expected to block this association.

Equilibrium associations were determined by UV/vis spectroscopy for 2,6-dichloropyridine-*N*-oxide (Figure 1) and for

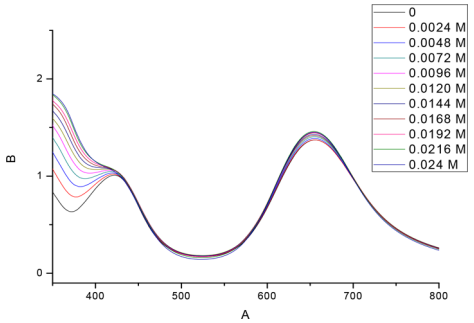
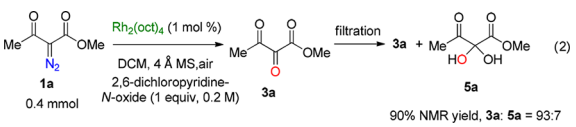


Figure 1. UV/vis spectrum for the coordination between 2,6-dichloropyridine-*N*-oxide and $Rh_2(oct)_4$. Spectral changes accompanying sequential additions of 2,6-dichloropyridine-*N*-oxide (0.30 M in DCM, from 0.20 to 2.0 equiv) to $Rh_2(oct)_4$ (1.20×10^{-2} M) in 2.5 mL of anhydrous DCM at 23 °C.

pyridine-*N*-oxide, with both exhibiting relatively low equilibrium constants (30.2 for **2b** and 43.2 for pyridine-*N*-oxide with $Rh_2(oct)_4$). Strikingly, however, 2,6-dichloropyridine-*N*-oxide **2b** showed no obvious spectral shifts by UV/vis spectroscopy or ^{1}H NMR spectroscopy, indicating negligible association with the dirhodium(II) catalyst. This confirmation of steric inhibition to association with dirhodium(II) carboxylate catalyst confirms that such bases can be used in rhodium(II) catalyzed reactions without inhibition of catalytic activity. 2,6-Dibromo- or 2,6-dimethyl-substituents do not offer any advantage over the 2,6-dichloro substituents.



Reactions with methyl diazoacetoacetate were performed at room temperature using a slight excess of the oxygen transfer agent. Treatment of MDAA with 2,6-dichloropyridine-*N*-oxide at room temperature in air produced only the anhydrous form of this 2,3-diketoester (>95%) in reactions performed in

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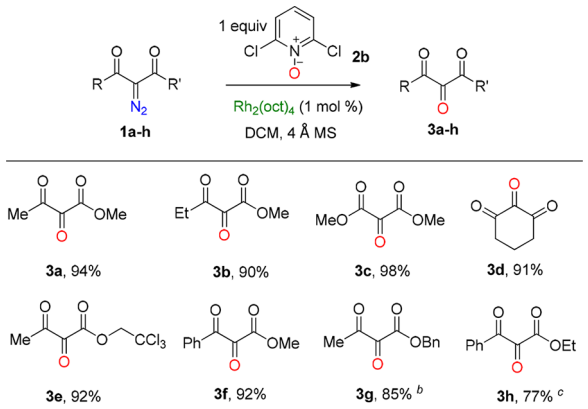
anhydrous solution. Upon standing the solution absorbed moisture, but this diketoester was isolated by filtration from molecular sieves through cotton in 90% yield with an anhydrous/hydrate ratio of 93:7. This level of the anhydrous form was similar to that which could be achieved by heating (90−100 °C) the hydrate of methyl 2,3-dioxobutanoate under vacuum (~1 Torr).[4]

Extension of the optimum conditions to other acceptor−acceptor diazo compounds showed the generality of the method (Scheme 2). Formation of the anhydrous tricarbonyl compound (**3**) was quantitative in most cases and was isolated in very high yield. The metal carbene intermediates formed from diazo compounds **1g** and **1h** underwent competing intramolecular reactions whose importance could be reduced with the use of excess 2,6-dichloropyridine-*N*-oxide.

Scheme 2. Oxygen Transfer of Acceptor−Acceptor Diazo Compounds[a]



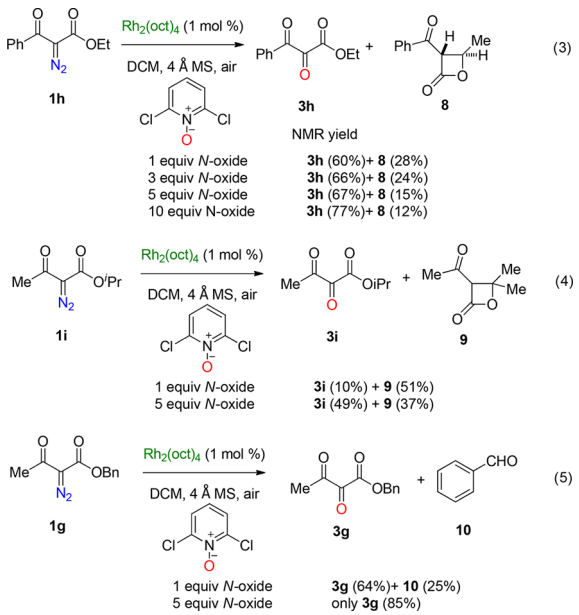
[a]4 Å Molecular sieves (50 mg) were added to a 1.0 mL DCM solution of **1a−h** (0.20 mmol) and 2,6-dichloropyridine-*N*-oxide (1.0 equiv). The mixture was stirred for 10 min before adding $Rh_2(oct)_4$ (2.00×10^{-3} mmol) at room temperature. Reactions were monitored by TLC. Yields were determined by ^1H NMR with 1,3,5-trimethoxylbenzene as the internal standard. [b]5 equiv of 2,6-dichloropyridine-*N*-oxide were used. [c]10 equiv of 2,6-dichloropyridine-*N*-oxide were used.

Competing reactions were intramolecular C−H insertion reactions (eqs 3 and 4) or a 1,4-hydrogen shift (eq 5) (Scheme 3). The formation of benzaldehyde by 1,4-hydride transfer is a known transformation[18] whose competition with oxygen transfer could be circumvented by increasing the relative amount of 2,6-dichloropyridine-*N*-oxide.

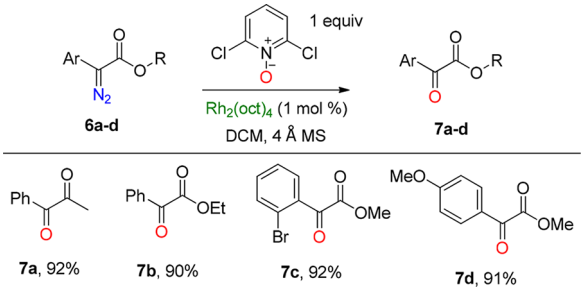
As expected, applications to donor−acceptor diazo compounds were similar in their quantitative conversions and high isolated yields (Scheme 4). The major difference from reactions with acceptor−acceptor diazo compounds was the relative ease in handling the tricarbonyl compounds, diketoesters being much less prone to hydrate formation.

2,3-Diketoesters have been employed in a number of transformations,[2,3] and representative reactions were run to determine if they could be successfully performed in the same reaction medium that is used to effect oxygen transfer. The ene reaction with α-methylstyrene (eq 6)[4] was performed on **3a** after completion of oxygen transfer. The asymmetric aldol reaction was performed on **3a** (eq 7) after completion of oxygen transfer by the addition of (L)-proline and cyclohexanone (Scheme 5).

Scheme 3. Competition Reactions for Some Specific Substrates

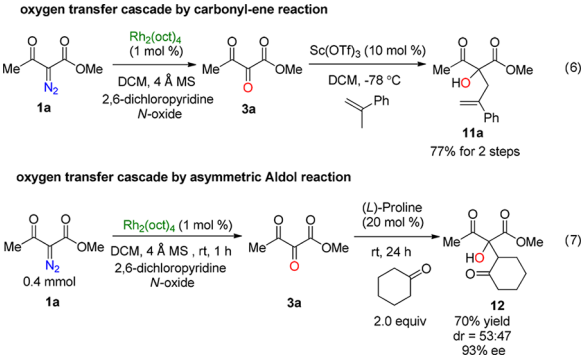


Scheme 4. Oxygen Transfer of Donor−Acceptor Diazo Compounds[a]



[a]4 Å Molecular sieves (50 mg) were added into a 1.0 mL DCM solution of **6a−d** (0.20 mmol), 2,6-dichloropyridine-*N*-oxide (1.0 equiv). The mixture was stirred for 10 min before adding $Rh_2(oct)_4$ (2.00×10^{-3} mmol) at room temperature. Reactions were monitored by TLC. Yields were determined as isolated yields after flash column chromatography.

Scheme 5. Applications in C−C Bond Forming Reactions



In summary, with catalysis by dirhodium carboxylates 2,6-dichloropyridine-*N*-oxide replaces dinitrogen by oxygen in diazocarbonyl compounds. In this general methodology, reactions occur at room temperature, produce the anhydrous

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di- and tricarbonyl compounds, form the basic 2,6-dichloropyridine that does not inhibit catalysis, and permit subsequent in situ transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03912.

Detailed experimental procedures, ^{1}H and ^{13}C NMR spectra of new compounds, and UV−vis spectra for coordination study (PDF)

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Notes

The authors declare no competing financial interest.

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