Synthesis of N-Acyl Pyrroles and Isoindoles from Oxime Ester Precursors via Transition Metal-Catalyzed Iminocarboxylation

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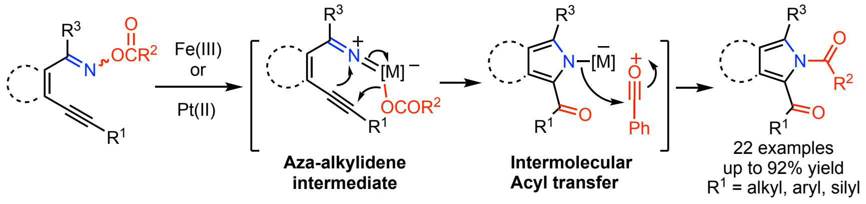
Special Issue Honoring Masahiro Murakami's Contributions to Science



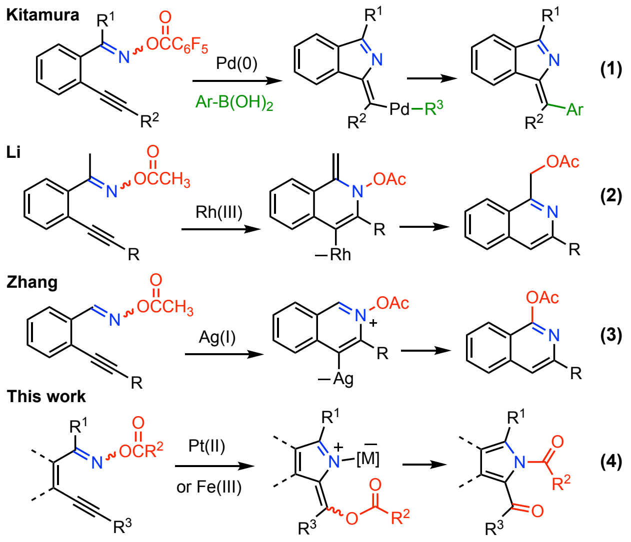
Received:
Accepted:
Published online:
DOI:

Abstract We describe Pt(II) or Fe(III)-catalyzed iminocarboxylation of oxime esters conjugated with 1,3-enyne and ortho-alkynyl arene moiety followed by a spontaneous O→N acyl migration of the enol carboxylate intermediate to generate N-acyl pyrroles and isoindoles. The reaction scope for pyrrole synthesis is general whereas the formation of isoindoles has a relatively narrow scope because of their instability.

Key words iminocarboxylation, pyrrole, isoindole, aza-alkylidene, oxime ester

Oxyamination[1] is a process whereby *N,O*-functionalities are added across the π-bond of alkene and alkyne usually catalyzed by transition metal complexes including, copper[2], iron[3], gold[4], platinum[5], palladium[6], rhodium[7], iridium[8], and osmium[9]. Compared to the oxyamination of alkenes, the corresponding oxyamination of alkynes is much less developed although some insightful examples of transition metal-catalyzed cyclization of alkyne-tethered oxime esters and oximes are reported (Scheme 1). Kitamura employed Pd(0)-catalyzed N–O bond cleavage with pentafluorobenzoyl oxime (eq 1).[10] The imino-Pd(II) complex undergoes *5-exo-dig* cyclization followed by capturing the vinyl-Pd(II) species with hydride or aryl boronic acid to generate methylene isoindole frameworks. Li reported that Rh(III) complex behaves as a p-philic Lewis acid to induce 6-*endo*-iminorhdation instead of N–O bond cleavage. The resulting *N*-acetoxy isoquinolinium intermediate undergoes thermal [3,3]-sigmatropic rearrangement to generate an isoquinoline derivative (eq 2).[11] Similarly, Zhang reported on the Ag-catalyzed reaction of aldoximes to generate *N*-acetoxy isoquinolinium intermediate which undergoes [1,2]-acetoxy migration followed by hydrolysis to provide isoquinolin-(2*H*)-ones (eq 3).[12] Shin explored Au(I)-catalyzed cyclization reactions of *E*/*Z*-isomeric oximes and found that (*E*)-oximes undergo iminoauration followed by proton transfer to generate isoquinoline-*N*-oxide.[13] On the other hand, the corresponding (*Z*)-oxime isomers selectively undergo oxyauration followed by N–O bond cleavage and C–N bond formation mediated by a-carbonyl Au-carbenoid to provide isoindole derivatives.

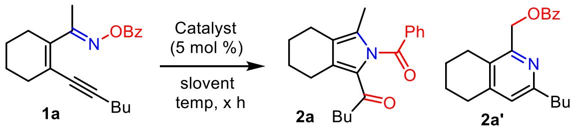
Scheme 1. Metal-catalyzed cyclization of alkyne-tethered oxime esters.



To expand the 1,2-difunctionalization of alkynes using metal-carbenoid, we turned our attention to the reactivity of metal-nitrenoid (eq 4)). The cyclization of *N*-acyloxycarbamates and *O*-acylhydroxamates catalyzed by Pt(II) or Fe(III) complex provided the initial amidocarboxylation products via metal-ketimido complex (aza-alkylidene). The characteristic reactivity of the enol carboxylate in these products entails O → N acyl migration leading to acyl pyrrole derivatives.[14]

We commenced our exploration with oxime ester to screen the variables. Treating **1a** with PtCl$_2$ (1 atm of CO, toluene, 65 °C) generated pyrrole **2a** in 84% yield (entry 1). Changing the solvent to dichloroethane gave a higher yield (entry 2). Replacing PtCl$_2$ with iron(III) or iron(II) catalysts also formed product **2a**, in slightly lower yields (entries 3–5). Lewis acid such as LiCl generated **2a** in moderate yield (50%). While gold (I) complexes Au(PPh$_3$)Cl gave **2a** in moderate yields the reaction with gold (III) complex dichloro(2-pyridinecarboxylato)gold led to decomposition of the substrate (entries 7 and 8). Among the catalyst tried, AgOTf showed unique reactivity to generate pyridine product **2a'** via 6-*endo* cyclization followed by [3,3]-sigmatropic rearrangement (entry 9). The reaction with Pd(PPh$_3$)$_4$ provided a moderate yield of **2a** (entry 10). Heating the substrate without a catalyst resulted in full recovery of the starting material, which rules out the thermal N–O bond cleavage pathway (entry 11).

Table 1. Optimization of conditions for iminocarboxylation followed O→N acyl group migration

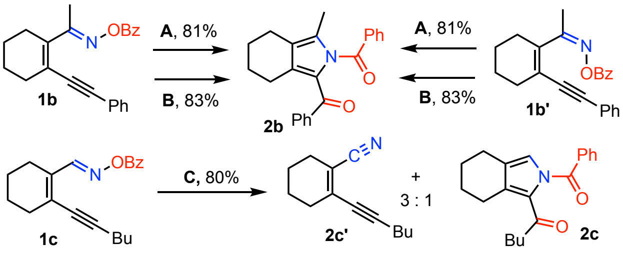


entry	catalyst	solvent	temp (°C)	time (h)	product	yield (%)[a]
1	PtCl$_2$/CO	toluene	65[b]	16	**2a**	84
2	PtCl$_2$/CO	ClCH$_2$CH$_2$Cl	65	20	**2a**	87
3	FeCl$_3$	CH$_3$CN	45	18	**2a**	78
4	Fe(acac)$_3$	CH$_3$CN	65	16	**2a**	78
5	FeBr$_2$	CH$_3$CN	45	24	**2a**	76
6	LiCl[c]	toluene	105	5.5	**2a**	50
7	Au(PPh$_3$)Cl	toluene	80	18	**2a**	63
8	Au(III)[d]	toluene	50	14	_[e]	—
9	AgOTf	CH$_2$Cl$_2$	60	12	**2a'**	65
10	Pd(PPh$_3$)$_4$	CH$_3$CN	75	3.5	**2a'**	48
11	None	toluene	65	24	_[f]	—

[a] Isolated yield. [b] At 100 °C, Complete conversion in 1 h. [c] 20 mol% loading. [d] Dichloro(2-pyridinecarboxylato)gold. [e] Decomposition. [f] No conversion.

The effect of oxime ester geometry[13] on the reaction course was examined with separately prepared (*E*)- and (*Z*)-oxime ester **1b** and **1b'** (Scheme 2). These oxime esters reacted smoothly and rendered the same product **2b** in similar yields. We also examined the reactivity of aldoxime **1c** and found that the formation of nitrile **2c'** is the major pathway over pyrrole **2c.**[10]

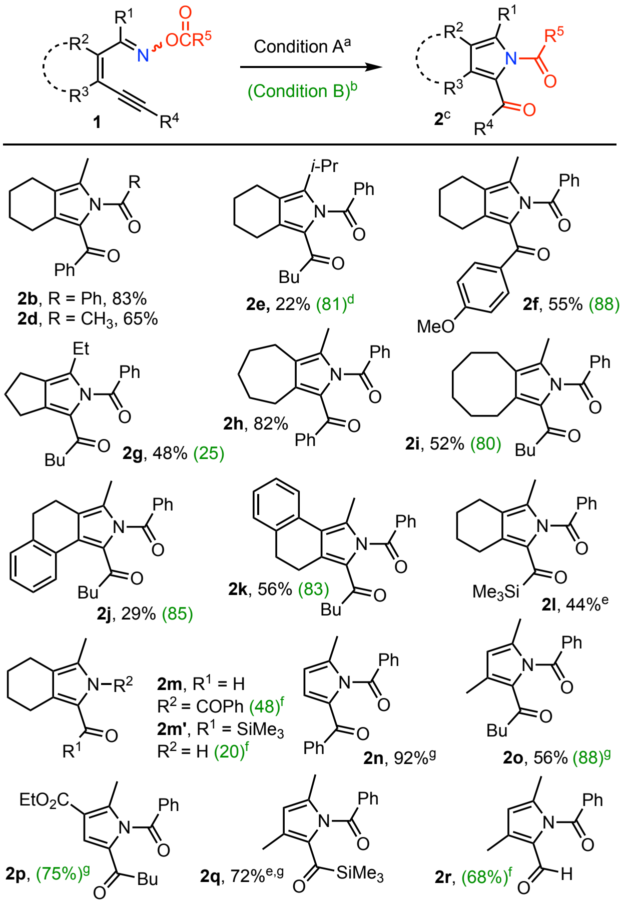
Scheme 2. Reactivity of E/Z-ketoximes and aldoximes



Conditions: A. PtCl$_2$/CO (5 mol%), DCE, 65 °C; B. FeCl$_3$ (5 mol%), MeCN, 45 °C; C. PtCl$_2$/CO (5 mol%), toluene, 65 °C.

With these reactivity profiles in hand, we further explored the generality with other substrates. Replacing the benzoyl group with the acetyl group gave a lower yield of **2d** but introducing different alkynyl substituents is well-tolerated to generate **2a**, **2b**, **2f,** and **2l** under the reaction conditions. The size of the fused ring has a significant impact on the reactivity; the substrate with a five-membered ring provided product **2g** in a much lower yield, while substrates with larger-sized rings gave good yields of the products **2h** and **2i**. The tetralone derivatives generate pyrroles **2j** and **2k** in high yields. The substrates without the fused ring also reacted smoothly, even in presence of the ester group to generate compounds **2n**, **2o,** and **2p**. Acyl silanes **2l** and **2q** were generated from the corresponding alkynyl silanes with iron catalyst while PtCl$_2$/CO provided a desilylated product with reduced yield. The increased water contents (20 equiv) in the reaction promoted desilylation, providing aldehydes **2m** and **2r** and deacylated product **2m'**.

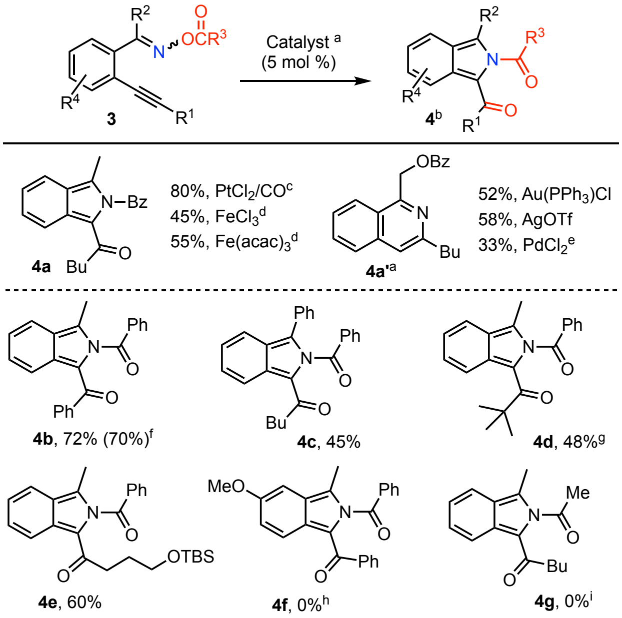
Table 2. Iminocarboxylation followed by acyl migration with cycloalkene and alkene-tethered substrates



[a] Condition A: FeCl$_3$ (5 mol%), MeCN, 45 °C, 18 h. [b] Condition B: PtCl$_2$/CO (5 mol%), dichloroethane, 65 °C, 20 h. [c] Yields of **2** are based on isolated material. [d] Yields in parenthesis are from the reaction using conditions B. [e] Reaction performed at 35 °C and monitored by TLC. [f] Obtained from silylated alkyne when the reaction was performed with 20 equiv of H$_2$O. [g] *E*/*Z*-mixture of oxime esters was used.

Next, we turned our attention to the reaction of benzo-fused oximes (Table 3).[15] While treating substrate **3a** with PtCl$_2$/CO provided **4a** in good yield, the reaction with iron(III) catalysts gave a much lower yield of the same product. On the contrary, Au, Ag and Pd catalysts provided isoquinoline **4a'** in moderate to low yields. Substrates with an aryl group or other alkyl group gave products **4b**, **4d**, and **4e** in good to moderate yields. On the other hand, the substrate with an electron-donating group on the fused benzene ring resulted in decomposition, thus **4f** was not generated. Also, replacing the benzoyl group with an acetyl group led to decomposition, and product **4g** was not obtained.

Table 3. Iminocarboxylation followed by acyl migration with arene-tethered substrates

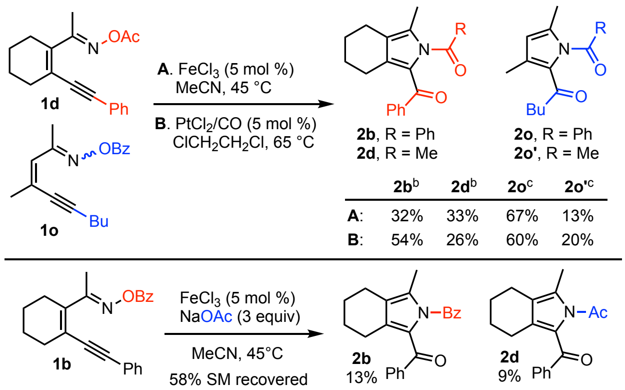


[a] PtCl$_2$/CO (5 mol%), dichloroethane, 65 °C, 15–24 h. [b] Isolated yields. [c] Reaction at 90 °C, 1 h. [d] MeCN, 45 °C. [e] Catalyst loading is 10 mol%. [f] *E*/*Z*-mixture of oxime esters. [g] Reaction performed at 75 °C. [h] No starting material was recovered. [i] 33% of starting material recovered.

To gain insight into the acyl transfer, we carried out a crossover experiment using two different oxime esters (Scheme 3). When the mixture of **1d** and **1o** (1:1 ratio) was treated with either Fe(III) or Pt(II) catalyst, four products (**2d**, **2o**, **2a**, and **2o'**) were obtained, including the acyl-exchanged products in different yields. Also, treating the oxime ester **1b** with FeCl$_3$ catalyst and NaOAc (3 equiv) provided pyrrole products **2b** and **2d** with low conversion in a normal time frame. These results suggest a bimolecular reaction mechanism for acyl transfer.

For the Pt(II)- and Fe(III)-catalyzed iminocarboxylation of oxime esters, we propose two plausible mechanisms that are consistent with the observed experimental data (Scheme 4). The first pathway involves an initial N–O bond cleavage of oxime ester **1/3** to form metal-ketimido complex[16] (aza-alkylidene) **IN-1**. The ketimido moiety in **IN-1** interacts with the alkyne to induce concomitant C–N and C–O bond formation to generate **IN-2**/**IN-3**, which undergoes acyl transfer to generate **2/4**. The acyl transfer likely involves the formation of an acylium ion, which is justified by the acyl group cross-over experiments. In the other pathway, the π-philic Lewis acid induces *5-exo-dig* cyclization to form **IN-4**, a resonance form of **IN-5**, which cyclizes to form **IN-6**. The N–O bond cleavage from **IN-6** to form **IN-7** followed by its reassociation with the catalyst will generate the same intermediate **IN-3**. Because p-philic Lewis acids induce *6-endo-dig* cyclization, and both *E*/*Z*-isomers of the oxime ester show similar reaction profiles, we conclude that the first pathway proceeding through ketimido complex (aza-alkylidene) is more consistent with the experimental outcomes.

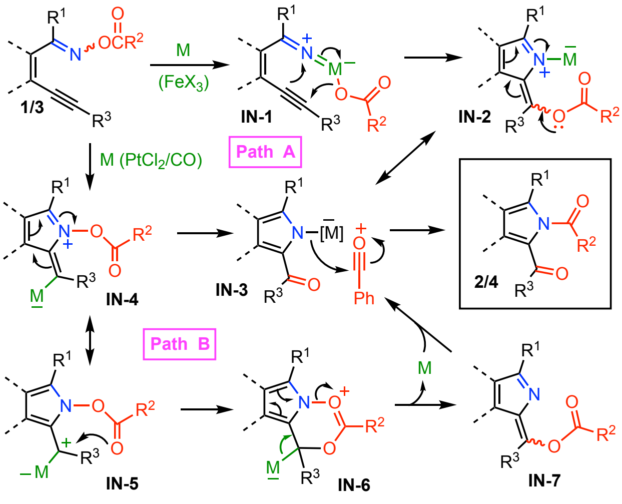
Scheme 3. Probing the intramolecular nature of acyl group transfer



	2b[b]	2d[b]	2o[c]	2o'[c]
A:	32%	33%	67%	13%
B:	54%	26%	60%	20%

[a] All yields are isolated yields. [b] Calculated by the quantity of **1d**. [c] Calculated by the quantity of **1o**.

Scheme 4. Mechanisms for iminocarboxylation and intramolecular O→N acyl transfer



In conclusion, we developed a unique protocol for the preparation of N-acyl pyrroles and isoindoles. Treating oxime esters conjugated with 1,3-enyne or alkynyl arene moiety with Pt(II) and Fe(III) catalyst induces iminocarboxylation to generate enol carboxylate products, which undergo spontaneous O→N acyl migration leading to *N*-acyl pyrroles and isoindoles. Mechanistically, we believe that the metal-ketimido complex (aza-alkylidene) is generated via initial N–O bond cleavage by a metal catalyst, which then undergoes concomitant C–N and C–O bond formation with the tethered alkyne followed by spontaneous acyl migration to complete the catalytic process.

The similar reactivity of both E/Z-isomers of the oxime ester is strong evidence that N–O bond cleavage precedes C–N bond formation. The reaction scope for pyrrole synthesis is general, which is exemplified by the formation of a novel acylsilane-containing pyrrole, whereas the formation of isoindoles has a relatively narrow scope because of their instability.

Funding Information

Authors thank NSF (CHE-2055055) for financial supports.

Acknowledgment

The Mass Spectrometry Laboratory at UIUC is acknowledged.

Supporting Information

YES

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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(17) **Procedure A**: The oxime ester (0.15 mmol) was dissolved in freshly distilled acetonitrile (2.5 mL) and taken into a Schlenk tube followed by the addition of $FeCl_3$ (0.075 mmol, 5 mol %). The reaction mixture was then sealed and heated at 45 °C until completion. The crude was concentrated *in vacuo* and purified by chromatography (SiO_2).

Procedure B: The oxime ester (0.15 mmol) was dissolved in freshly distilled toluene (3 mL) and taken into the Schlenk tube followed by the addition of $PtCl_2$ (0.075 mmol, 5 mol %). Then carbon monoxide was gradually bubbled into the solution for 10 min. The Schlenk tube was then carefully sealed and heated at 65 °C – 70 °C until completion. The crude was concentrated *in vacuo* and purified by chromatography (SiO_2).

Characterization of 2a: 1H NMR (500 MHz, CDCl3) δ 7.56 (d, J = 7.6 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.7 Hz, 2H), 2.85 (t, J = 6.2 Hz, 2H), 2.53 (t, J = 7.5 Hz, 2H), 2.49 (t, J = 6.2 Hz, 2H), 2.10 (s, 3H), 1.89 – 1.82 (m, 2H), 1.82 – 1.74 (m, 2H), 1.46 (p, J = 7.6 Hz, 2H), 1.18 (h, J = 7.4 Hz, 2H), 0.81 (t, J = 7.3 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 188.61, 171.65, 135.32, 133.61, 133.12, 130.56, 129.45, 129.13, 128.51, 120.47, 39.47, 26.52, 24.47, 23.41, 22.83, 22.36, 21.41, 13.88, 10.08; HRMS (ESI) calcd for $[M+H]^+$ 324.1964, found 324.1962.