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Promoting Reductive Tandem Reactions of Nitrostyrenes with $Mo(CO)_6$ and a Palladium Catalyst To Produce 3*H*-Indoles

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Supporting Information

ABSTRACT: The combination of $Mo(CO)_6$ and 10 mol % of palladium acetate catalyzes the transformation of 2-nitroarenes to 3*H*-indoles through a tandem cyclization-[1,2] shift reaction of in situ generated nitrosoarenes. $Mo(CO)_6$ appears to have dual roles in this transformation: generate CO and promote C−N bond formation to increase the yield of the N-heterocycle product.

The potential of triggering carbon−nitrogen bond formation using a nitro-group as the source of the nitrogen atom inspires significant research because of the widespread availability of nitroarenes.[1] These research efforts have eased the transformation of nitroarenes into indoles and carbazoles by forming sp^2-C−N bonds from sp^2-C−H bonds.[2] This C−H bond amination is traditionally achieved using superstoichiometric quantities of a reductant such as phosphite,[3] zinc dust,[4] Grignard reagent,[5] or high pressures of carbon monoxide,[6] which convert the nitro-group into an electrophilic nitrogen species. In contrast, creating partially saturated, nonplanar N-heterocycles from nitroarenes has been slow to emerge,[7] and these processes are traditionally typified by low yields and significant byproduct formation.[8] Our group has developed transition-metal-catalyzed methods to convert aryl azides into complex, functionalized N-heterocycles through an electrocylization−migration tandem reaction of rhodium *N*-aryl nitrene **2** (Scheme 1).[9] During the course of our studies, we were curious if spirocyclic heterocycles—inaccessible from aryl azides using our methods—could be formed from nitroarenes. Herein, we report that the reactivity embedded in trisubstituted nitrostyrenes can be unlocked using $Mo(CO)_6$ and a palladium catalyst to enable access to functionalized 3*H*-indoles.

Scheme 1. Rh_2(II)-Promoted Tandem Reactions

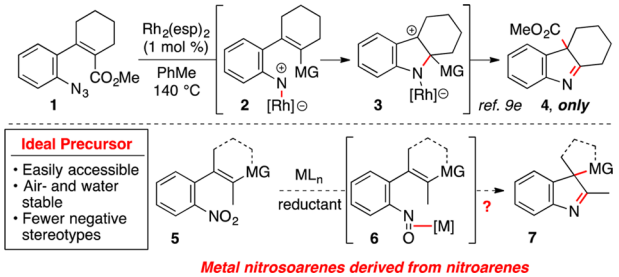
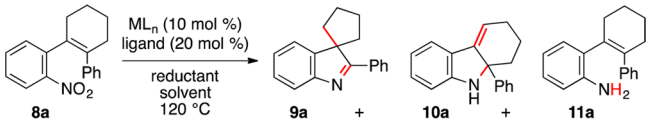


Table 1. Development of Optimal Conditions



entry	catalyst	ligand	reductant	solv	yield, %[a] 9:10:11
1[b]	$Pd(OAc)_2$	phen	CO (1.5 atm)	DMF	20:40:0
2[b]	$Pd(OAc)_2$	tmphen	CO (1.5 atm)	DMF	12:21:0
3[b]	$Pd(TFA)_2$	phen	CO (1.5 atm)	DMF	44:8:0
4[b,c]	$Pd(TFA)_2$	phen	CO (1.5 atm)	DMF	62:0:0
5[b,c]	$Pd(TFA)_2$	phen	CO (3 atm)	DMF	37:0:0
6[d]	$Pd(OAc)_2$	phen	$Mo(CO)_6$	DMF	30:0:35
7[d]	$Pd(OAc)_2$	phen	$Mo(CO)_6$	THF	48:0:50
8[d]	$Pd(OAc)_2$	phen	$Mo(CO)_6$	DCE	80:0:0
9[e]	$Pd(OAc)_2$	phen	$Mo(CO)_6$	THF	16:15:38
10[f]	$Pd(OAc)_2$	phen	$Mo(CO)_6$	DCE	68:0:0

[a]As determined using ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard. [b]20 mol % of $Pd(OAc)_2$ and 40 mol % ligand used. [c]0.4 equiv of trifluoroacetic acid added. [d]1.0 equiv of $Mo(CO)_6$ used. [e]0.5 equiv of $Mo(CO)_6$ used. [f]5 mol % of $Pd(OAc)_2$ and 10 mol % phen used.

To determine if a cyclization−migration cascade could be triggered, nitroarene **8a** was examined toward transition-metal catalysts and reductants (Table 1). The substrate for our study was easily constructed by cross-coupling the commercially available 2-nitrophenylboronic acid with the vinyl triflate derived from 2-phenylcyclohexanone. At the outset of our study, nitroarene **8a** was exposed to a range of different transition-metal complexes using 1.5 atm of carbon monoxide as the reductant. To our dismay, examination of common Rh-,[10] Ru-,[7a,10a] and Pt-catalysts[11] for the reduction of nitroarenes produced only aniline **11a**. In contrast, in situ generated phenanthroline palladium(II) complexes triggered the desired cyclization (entry 1).[6] Unfortunately, the migration step was short-circuited by deprotonation to result in both spirocycle **9a** and indoline **10a**. Changing the identity of the phenanthroline ligand did not improve the ratio of spirocycle **9a** to **10a** (entry 2).[10b,12b] Deprotonation could be inhibited by using $Pd(TFA)_2$ as the precatalyst (entry 3), and the addition of trifluoroacetic acid further improved both the yield and selectivity of the reaction (entry 4). Increasing the pressure of CO proved detrimental to this result (entry 5). In an attempt to improve the

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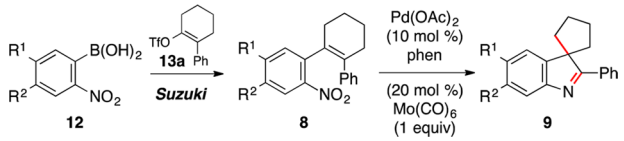
Table 2. Examination of the Electronic Nature of the Nitroarene



entry	no.	R^1	R^2	R^3	9 yield, %[a,b]
1	a	H	H	H	77
2	b	MeO	H	H	60 (82)[c]
3	c	Me	H	H	64
4	d	F	H	H	72
5	e	F_3C	H	H	54[c]
6	f	H	MeO	H	68
7	g	H	Me	H	77
8	h	H	F	H	88
9	i	H	CO_2Me	H	75

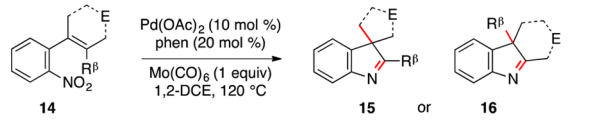
[a]Conditions: 10 mol % $Pd(OAc)_2$ 20 mol % phenanthroline, $Mo(CO)_6$ (1 equiv), DCE, 120 °C, 16 h. [b]Isolated after silica gel chromatography. [c]20 mol % $Pd(OAc)_2$ used.

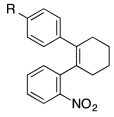
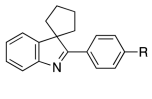
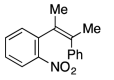
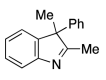
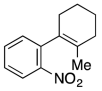
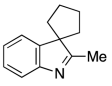
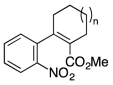
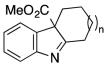
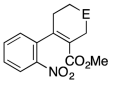
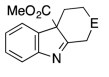
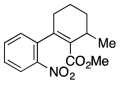
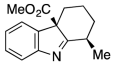
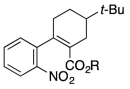
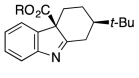
yield of our transformation, alternative sources of CO were screened. Metal carbonyl complexes are well established to release CO upon heating,[13] and $Mo(CO)_6$ is a proven CO equivalent in palladium-catalyzed carbonylation reactions.[14] To our delight, when CO source was changed to $Mo(CO)_6$, neither the deprotonation product **10a** nor oligomerization was observed (entries 6–8). Dichloroethane was found to be the optimal solvent enabling clean formation of spirocycle **9a** in 80% without any observed aniline byproduct (entry 8). Both aniline **11a** and **10a** byproducts were observed, however, when the amount of $Mo(CO)_6$ was reduced from 1 to 0.5 equiv (entry 9). In contrast, reducing the catalyst loading of $Pd(OAc)_2$ and phenanthroline proved less detrimental, while the yield of spirocycle **9a** was attenuated to 68%, no byproducts were formed (entry 10).

Using these optimal conditions, we examined the scope and limitations of palladium-catalyzed reductive cyclization–migration reaction (Table 2). This investigation was significantly eased by the modular nature of our substrate synthesis, which enables rapid construction of nitroarenes through a Suzuki cross-coupling reaction between 2-nitroarylboronic acid **12** and vinyl triflate **13a**. First, the effect of changing the nitroarene substituent was examined. To our delight, we found that our reaction tolerated a range of electron-releasing or electron-withdrawing aryl R^1-substituents without significant attenuation the yield (entries 1–5). Next to demonstrate that our reaction enables access to 3*H*-indoles, which cannot be formed as single isomers using Fischer-indole-type reactions,[15] the identity of the R^2-substituent was changed. Spirocycle **9** was formed smoothly irrespective of the electronic identity of the substituent (entries 6–9).

Next, the scope of the reaction was surveyed by varying the identity of the *o*-alkenyl substituent of the nitroarene (Table 3). First, higher yields were obtained with electron-rich R^{β}-aryl substituent (entries 1 and 2). In contrast to the expected alkyl shift, untethering the α- and β-alkyl substituents in **14c** triggered a [1,2] phenyl shift to form 3*H*-indole **15c** (entry 3). Next, the effect of changing the identity of the R^{β}-substituent was investigated (entries 4–12). While ring contraction was observed with an R^{β}-methyl to afford spirocycle **15d** (entry 4), switching to a carboxylate group changed the identity of the product to 3*H*-indole **16** (entry 5). Carboxylate migration was not dependent on the ring size of the *ortho*-substituent: six-, seven- and even eight-membered cycloalkenyl substrates could be smoothly converted to 3*H*-indole **16** (entries 5–7). Next, changing the composition of the tether was examined (entries 8–9): 3*H*-indoles could be accessed from nitroarenes **14h** and **14i** bearing *ortho*-heterocycle substituents if a higher catalyst loading was used. The diastereo-selectivity of our reaction was next probed.

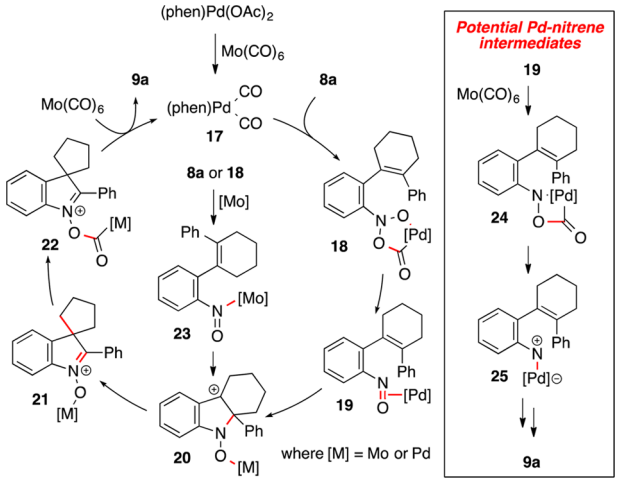
Table 3. Scope and Limitations of 3*H*-Indole Formation



entry	#	nitroarene	3*H*-indole	yield, %[a]
1	a			76, R = OMe
2	b			48, R = CF_3
3	c			59
4	d			49(54)[b]
5	e			73, n = 1
6	f			52, n = 2
7	g			56, n = 3
8	h			67, E = O[b]
9	i			59, E = NBoc[b]
10	j			65 d.r. 91:9
11	k			45, d.r. 80:20 R = Me
12	l			49, d.r. 90:10 R = *t*-Bu

[a]Isolated after silica gel chromatography. [b]20 mol % $Pd(OAc)_2$ used.

Scheme 2. Possible Mechanism for 3H-Indole Formation



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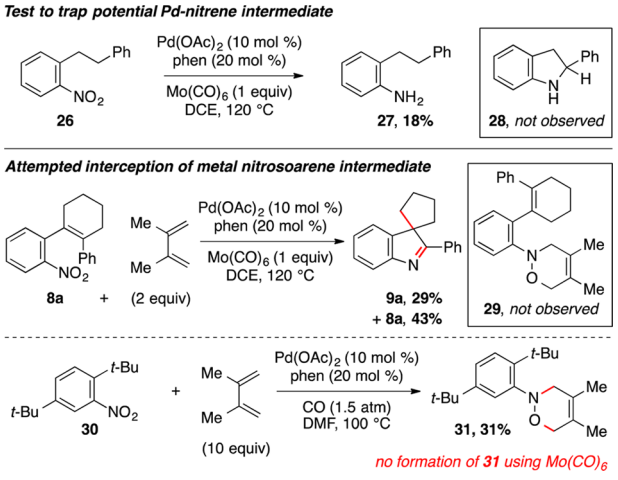
The allylic methyl group in **14j** directed the stereoselectivity of the transformation to afford 3*H*-indole **16j** as a 91:9 mixture of diastereomers (entry 10). Moving the stereocenter to the homoallylic position in **14k** attenuated the diastereoselectivity slightly to 80:20 (entry 11). This ratio could be improved by increasing size of the migrating group to a *tert*-butyl carboxylate (entry 12).

Our initial mechanistic hypothesis for 3*H*-indole formation is based on the previous investigations into the catalytic cycle of palladium-mediated nitroarene reduction (Scheme 2).[12,16] Reduction of (phen)Pd(OAc)$_2$ complex by Mo(CO)$_6$ would produce the palladium CO complex **17**, which could exist either as a monomer or a cluster.[17] Oxidative addition of nitroarene produces palladacycle **18**.[18] Reductive elimination of CO_2 produces palladium-nitrosoarene **19**. Cyclization of **19** could occur through electrocyclization or attack by the adjacent π-system.[19] The resulting benzylic cation in **20** triggers a ring contraction to produce spirocycle *N*-oxide **21**. Reduction produces 3*H*-indole **9a** and regenerates the palladium−carbonyl catalyst. Alternatively, Mo(CO)$_6$ could have multiple functions: in addition to serving as the CO-source for Pd-catalyzed N−O bond reduction, it could coordinate to nitrosoarene **23** to facilitate attack by the pendant olefin to afford **20**.[20] A third possible mechanism is that spirocycle formation occurs via a metal nitrene intermediate. These intermediates have been posited as potential catalytic intermediates in related processes:[7,8] a ruthenium nitrene was implicated by Cenini and coworkers in their intermolecular allylic C−H bond amination of cyclohexene with nitroarenes.[7a] Palladium nitrosoarene complex could be reduced to produce palladacycle **24**.[21] Reductive elimination of CO_2 then produces palladium nitrene **25**, which could undergo a 4π-electron-5-atom-electrocyclization-ring contraction to produce the 3*H*-indole product.

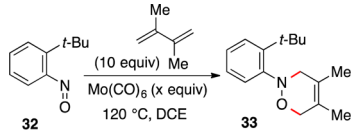
Several experiments were performed to distinguish between these possible mechanisms (Scheme 3).[22] First, we submitted

Scheme 3. Attempted Interception of Catalytic Intermediates



nitroarene **26** to reaction conditions to examine if palladium nitrene **25** was a catalytic intermediate. We expected that if this intermediate was formed that some 2-phenylindoline would be observed.[23] In contrast, only aniline was produced to suggest that metal nitrenes are not catalytic intermediates. Next, interception of the nitrosoarene intermediate was attempted through the addition of 2,3-dimethylbutadiene to the reaction mixture.[24] To our surprise, the putative nitrosoarene could not be trapped from either nitroarene **8a** or 2,5-di-*tert*-butylnitrobenzene using Mo(CO)$_6$. It could only be intercepted from **30** using CO as the reductant to produce oxazine **31**.

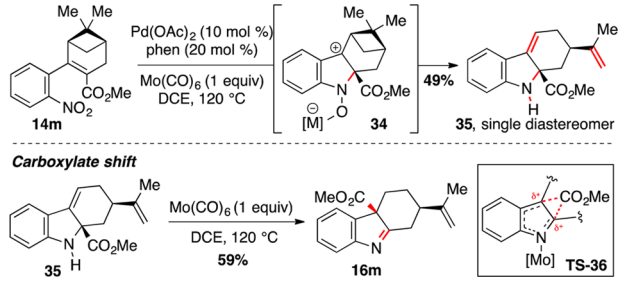
To further investigate the effect of Mo(CO)$_6$, the reactivity of 2-*tert*-butylnitrosobenzene **32** was examined (Eq 1). As expected, exposure to 2,3-dimethylbutadiene resulted in formation of oxazine **33**. The addition of Mo(CO)$_6$, however, completely inhibited cycloaddition—irrespective of the equivalents of butadiene or 1,5-cyclooctadiene present—leading to aniline. Together these experiments indicate that Mo(CO)$_6$ is not simply functioning as a source of CO, but that it coordinates the nitrosoarene to induce cyclization and migration.[20] Because Pd(OAc)$_2$ is required for high yields,[25] our data suggests that role of the palladium phenanthroline complex is to catalyze the N−O bond reduction in nitroarene **8a** and spirocycle **21**.[26]



Mo(CO)$_6$	33	aniline
none	98%	
1 equiv	0%	15%
1 equiv + 1,5-COD (1 equiv)	0%	39%

Further insight into the mechanism was serendipitously provided by α-pinene-derived nitroarene **14m** (Scheme 4). Exposure of this nitroarene to reaction conditions produced only indoline **35** as a single diastereomer. The expected 1,2-carboxylate migration was short-circuited by deprotonation of one of the bridgehead methyl groups in **34** inducing a fragmentation to produce **35**.[27] We found that the migration of the methyl carboxylate did not require palladium: exposure of indoline **35** to Mo(CO)$_6$ formed 3*H*-indole **16m** as a single diastereomer.[28] The chemoselectivity of this migration step appears to result from the transition state or intermediate containing the more stable iminium ion (e.g., **TS-36**).

Scheme 4. Separation of Cyclization and Migration Steps



In conclusion, we have shown that the combination of palladium acetate and Mo(CO)$_6$ can unlock the reactivity embedded in 2-alkenyl-substituted nitroarenes and trigger cyclization−migration reactions to produce spirocyclic 3*H*-indoles. Our future studies are aimed at further exploring the reactivity of palladium nitrosoarene complexes to produce complex, functionalized N-heterocycles from readily accessible 2-substituted nitroarenes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic and analytical data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02946.

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Notes

The authors declare no competing financial interest.

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J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

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