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Control of the Chemoselectivity of Metal *N*-Aryl Nitrene Reactivity: C−H Bond Amination versus Electrocyclization

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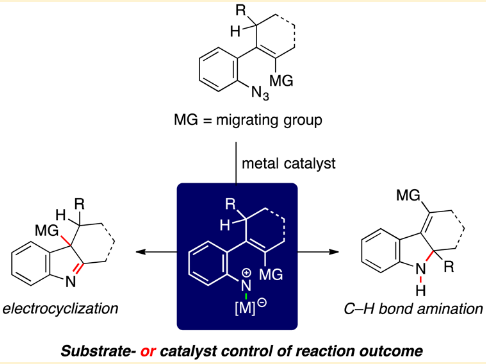
Supporting Information

ABSTRACT: A mechanism study to identify the elements that control the chemoselectivity of metal-catalyzed N-atom transfer reactions of styryl azides is presented. Our studies show that the proclivity of the metal *N*-aryl nitrene to participate in sp^3-C−H bond amination or electrocyclization reactions can be controlled by either the substrate or the catalyst. Electrocyclization is favored for mono-*β*-substituted and sterically noncongested styryl azides, whereas sp^3-C−H bond amination through an H-atom abstraction−radical recombination mechanism is preferred when a tertiary allylic reaction center is present. Even when a weakened allylic C−H bond is present, our data suggest that the indole is still formed through an electrocyclization instead of a common allyl radical intermediate. The site selectivity of metal *N*-aryl nitrenes was found to be controlled by the choice of catalyst: Ir(I)-alkene complexes trigger electrocyclization processes while Fe(III) porphyrin complexes catalyze sp^3-C−H bond amination in substrates where Rh_2(II) carboxylate catalysts provide both products.



■ INTRODUCTION

Achieving absolute control over the product distribution of a catalytic reaction continues to be vigorously pursued by synthetic chemists. While significant progress has been made across many reaction types to access different scaffolds from the same starting materials and reagents by manipulating the identity of the catalyst,[1,2] this control remains elusive in C−H bond amination reactions and remains an important and largely unrealized goal.[3] The reactivity patterns of metal nitrenes have been exploited to create new C−N bonds from C−H bonds and *π*-systems,[1] and to date, the advances in these fields have been largely driven using nitrenes substituted with a strong electron-withdrawing group (Scheme 1).[4−9] These investigations have established chemoselectivity trends,[3] which permit the use of these C−H bond aminations in target-oriented syntheses.[10] In contrast, these preferences remain unknown for metal *N*-aryl nitrenes despite the prevalence of the resulting aryl amines and *N*-heteroaromatics in pharmaceuticals and materials.[11−13] As an additional complication, metal *N*-aryl nitrenes also react with adjacent *π*-systems through electrocyclization processes to produce *N*-heteroaromatics.[14] Understanding and controlling the reactivity of metal *N*-aryl nitrenes to participate in an electrocyclization or C−H bond amination reaction is critical to the rational design of target-oriented syntheses that use this reaction at a late stage to install the valuable *N*-aryl moiety, which is ubiquitous in indole alkaloids,[15] as well as the design of new reactions that harness the reactivity of metal *N*-aryl nitrenes. This understanding will only emerge from studying systems that contain multiple potential sites of reaction,[16] and applying the conclusions into the origin of reactivity preferences to control reaction outcomes.

Our investigations into the reactivity of *ortho*-substituted aryl azides toward Rh_2(II) carboxylate complexes revealed that certain substrates preferred to undergo sp^3-C−H bond amination instead of the expected electrocyclization domino reaction (Scheme 2).[17−19] Exposure of *β*-acyl trisubstituted styryl azides to $Rh_2(esp)_2$ triggered an electrocyclization-acyl migration domino reaction to produce 1,2,3-trisubstituted indoles, such as **9**, from azides **8**.[20] In the absence of catalyst, no reaction occurred. We found that the identity of the *α*-substituent impacted the identity of the product. When the substrate contained an *α*-aryl or *α*-*n*-alkyl group, the expected 1,2,3-trisubstituted indole was obtained as the only product. Introduction of a tertiary C−H bond into the *α*-position, however, changed the outcome of the reaction. Instead of an electrocyclization−migration domino reaction, allylic C−H bond amination was observed to produce indoline **13** from styryl azide **12**.

In our studies into 3*H*-indole formation,[21,22] the presence of a tertiary allylic C−H bond was also found to change the course of Rh_2(II)-catalyzed amination reactions (Scheme 3). While electrocyclization−migration was observed with styryl azide **16**

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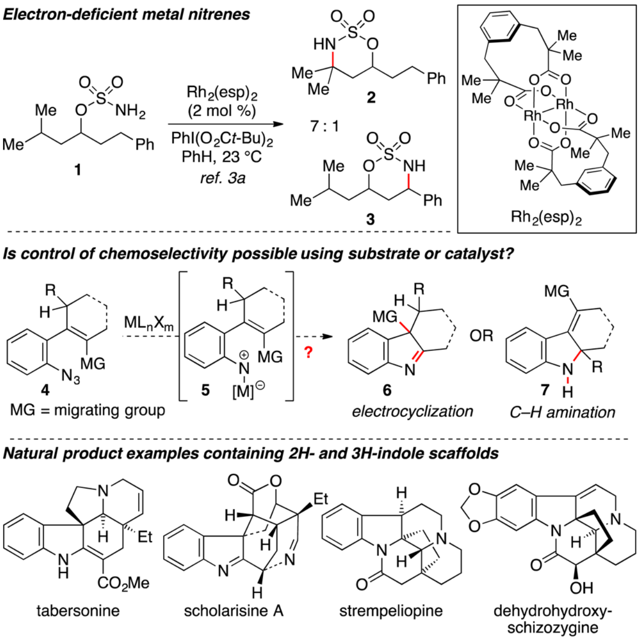
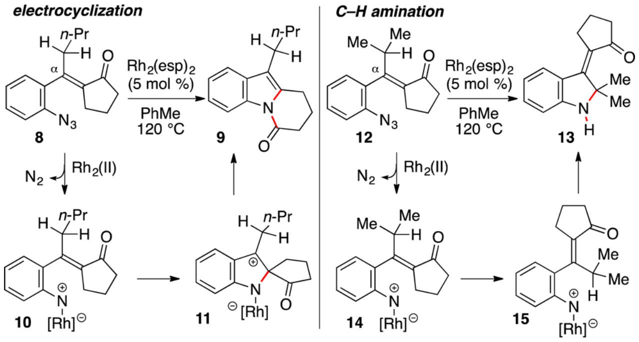
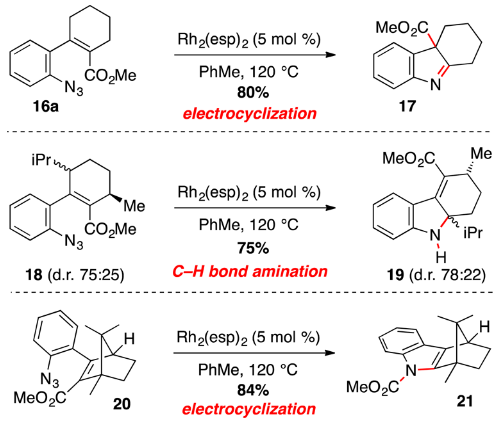
Scheme 1. Substrate versus Catalyst Control of the Chemoselectivity of the Metal Nitrene Catalytic Intermediate



Scheme 2. Observation of an sp^3-C–H Bond Amination in Lieu of Electrocyclization–Migration Reaction



Scheme 3. Observation of an sp^3-C–H Bond Amination in Lieu of Electrocyclization–Migration Reaction

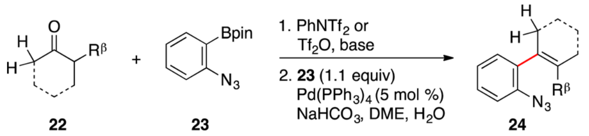


to afford 3H-indole **17**,[21] exclusive sp^3-C–H bond amination was observed from submission of menthol-derived azide **18** (3:1 mixture of diastereomers) to reaction conditions to produce 2H-indole **19** as a 3.5:1 mixture of diastereomers. The preference for electrocyclization–migration could be restored by conformationally locking the tertiary allylic C–H bond: exposure of camphor-derived styryl azide **20** to Rh$_2$(esp)$_2$ smoothly converted it to indole **21** through an electrocyclization followed by migration of the methyl carboxylate to the nitrogen atom.[22]

Our curiosity was piqued by these unexpected sp^3-C–H bond amination products, and at the conclusion of these studies, we wanted to systematically probe the effect that the *ortho*-substituent had on the outcome of the amination reaction in order to establish a predictive model. Toward that end, we decided to examine substrates that would examine the relationship between the steric and the electronic environment of the two potential reaction centers to determine their impact on whether allylic C–H bond amination or electrocyclization took place. In addition to investigating substrate control over the reaction outcome, we also wanted to determine if catalysts could overcome the inherent substrate preference.

■ RESULTS AND DISCUSSION

Investigation into Substrate Control of Reaction Outcome. To find examples where allylic C–H bond amination occurred in the absence of a tertiary sp^3-C–H bond, the reactivity of a series of styryl azides toward Rh$_2$(II)-carboxylate catalysts was examined. These substrates were assembled in two steps from the β-ketoester through a cross-coupling sequence using 2-azidobenzene-boronic pinacolate ester **23** to introduce the aryl azide portion using conditions developed in our laboratory (eq 1).[23] The resulting styryl azides



(1)

were exposed to 5 mol % of Rh$_2$(esp)$_2$ (Table 1). In the absence of catalyst, no reaction occurred. Styryl azides bearing cyclic enone *ortho*-groups were converted into indoles **26a** and **26b** irrespective of the identity of the β-substituent (entries 1 and 2). While piperidone-derived styryl azide **24c** afforded the 3H-indole electrocyclization product (entry 3),[21] 3-oxoproline-derived **24d**, containing an in conjugation N-Boc carbamate, produced the secondary allylic C–H bond amination heterocycle **26d** as the only product, albeit in reduced yield (entry 4). Together with entries 1 and 2, these results show that introduction of an additional carbonyl- or N-Boc carbamate β-substituent makes the electrocyclization pathways energetically unfavorable by weakening the allylic C–H bond to produce heterocycles from exclusive C–H bond amination. Carbon–hydrogen bond dissociation energies are significantly lower when an α-amine or carbonyl is present.[24,25] In these styryl azides this weakening would be transmitted through the π-system to weaken the allylic C–H bond and enable amination to occur. While no reaction was observed when a primary β-amide-substituted styryl azide was submitted to reaction conditions (entry 5), exposure of the secondary amide **24f** produced indole **26f**; no products of electrocyclization–migration were observed (entry 6). Because this amide should not have a larger effect on the bond strength than the β-carboxylate, we interpret this result to mean that the electrocyclization is also disfavored due to increased steric

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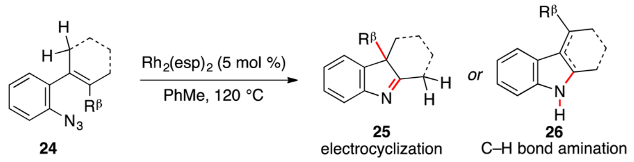
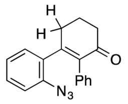
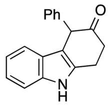
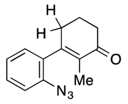
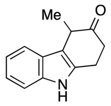
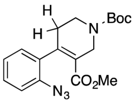
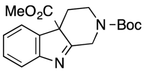
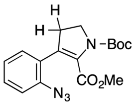
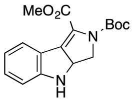
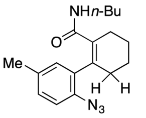
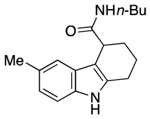
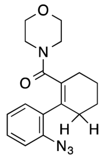
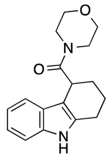
Table 1. Allylic C−H Bond Amination versus Electrocyclization



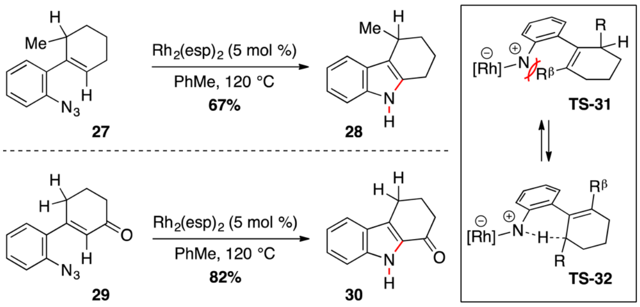
entry	#	styryl azide	N-heterocycle	yield, %[a]
1	a			84
2	b			85
3	c			84[b]
4	d			48
5	e			n.r.[c]
6	f			26

[a] Isolated after silica gel chromatography. [b] From ref 21. [c] Decomposition occurred when the reaction mixture was heated to 140 °C.

interactions that arise when the carboxylate is replaced with an amide.

Next, the effect of changing the steric environment at the electrocyclization reaction site was examined (Scheme 4). For this study, we chose to examine styryl azidess (e.g., **18** and **24a**) where allylic C−H bond amination was observed and replace the *β*-substituent with a hydrogen to determine whether the preference for electrocyclization could be restored. In styryl azide **27**, the *β*-methyl carboxylate substituent was removed while the tertiary allylic C−H bond was retained; whereas in styryl azide **29**, the alkyl- or phenyl *β*-substituents were replaced with hydrogen. Exposure of **27** and **29** to reaction conditions produced only electrocyclization product, indoles **28** and **30**. The results of these two azides reveal the sensitivity of the electrocyclization on the steric environment of the *ortho*-alkenyl substituent. We rationalize these outcomes on the presence of a *β*-substituent, which will introduce destabilizing steric interactions with the rhodium *N*-aryl nitrene since a 5-atom-4-*π*-electron electrocyclization requires a planar transition state for bond formation.[26] We believe that these steric interactions will raise the energy of the electrocyclization transition state (**TS-31**) to make the allylic C−H bond amination reaction (accessible through the H-atom transfer transition state **TS-32**). The destabilizing steric interactions in **TS-31** are minimized when the R^{β}-substituent is hydrogen to favor electrocyclization to produce the *N*-heterocyclic product.

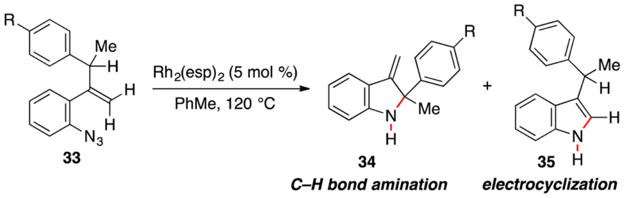
Scheme 4. Effect of Changing the Steric Environment on the Reaction Outcome



We anticipated that further insight into the competitive nature of these two mechanisms could be gained from studying substrates that afforded a mixture of the electrocyclization and C−H bond amination products. To make C−H bond amination competitive with electrocyclization on a sterically accessible alkenyl unit, we replaced one of the tertiary allylic alkyl groups with an aryl group. The presence of the aryl group in aryl azide **33** would enable us to examine the effect of changing the electronic environment of the sp^3-C−H allylic site on the ratio of electrocyclization to sp^2-C−H bond amination. The resulting substituent effect should be limited to only affecting the $\Delta G^{\ddagger}$ of C−H bond amination because the benzyl methine insulates the alkene *π*-system.

In line with these expectations, exposure of styryl azide **33** to reaction conditions produced a mixture of the C−H bond amination product, 2*H*-indole **34**, and the electrocyclization-migration product, indole **35** (Table 2). We found that as the R-substituent became more electron-withdrawing, the amount of allylic C−H bond amination was diminished. A correlation was observed when the product ratios were plotted against Hammett σ_{para} constants (Figure 1).[27] While increasing the electron-deficiency of the aryl substituent favored the electrocyclization, a slight increase in the slope of the line was observed when the electron-releasing substituent was replaced with an electron-withdrawing substituent. This correlation

Table 2. Effect of Changing the Electronic Nature of the Allylic C−H Bond on the Reaction Outcome



entry	#	R	σ_{para}[a]	σ_{mb}[b]	$\sigma_{JJ}^{\bullet}$[b]	34:35	yield, %[c]
1	a	OMe	−0.27	−0.77	0.23	1:4	83
2	b	Me	−0.17	−0.29	0.15	1:5.1	94
3	c	H	0	0	0	1:5.8	82
4	d	F	0.06	−0.24	−0.02	1:10.7	66
5	e	Cl	0.23	0.11	0.22	1:13.0	56
6	f	OCF_3	0.35	–	–	1:83	84

[a] From ref 27. [b] From ref 34b. [c] As determined using ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard.

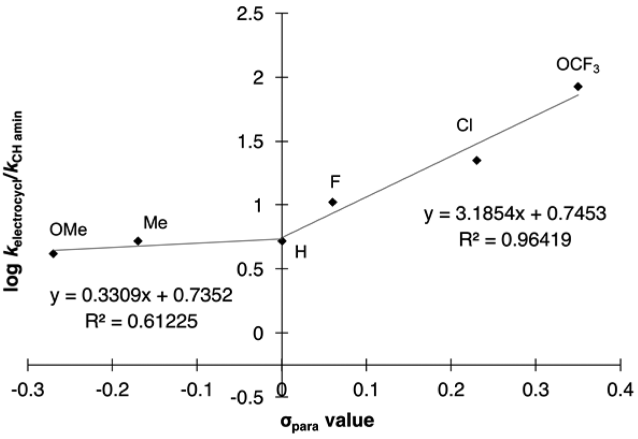


Figure 1. Effect of changing the electronic environment at the allylic C−H bond reaction center: correlation of heterocycle product ratios with Hammett σ_{para} values.

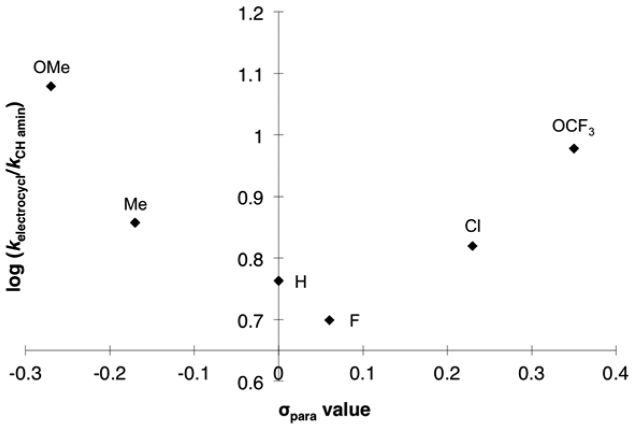
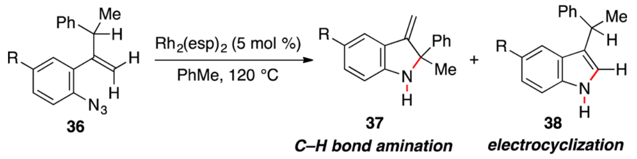


Figure 2. Effect of changing the electronic environment of the rhodium *N*-aryl nitrene: correlation of heterocycle product ratios with Hammett σ_{para} values.

appears to consist of two intersecting lines: the effect of electron-releasing substituents exhibits a smaller ρ-value (0.33) than that of electron-withdrawing groups, which display a larger ρ-value of 3.18 to imply a larger buildup of charge at the benzyl carbon for these substrates. The intersecting lines also indicate that a change of mechanism or a change in the rate-determining step is also occurring.

Next, using this scaffold, the identity of the 4-substituent on the aryl azide moiety was modified to gain insight into the effect of changing the electronic nature of the rhodium *N*-aryl nitrene on the outcome of the reaction (Table 3). For styryl azides **36**, the presence of either an electron-donating- or -withdrawing substituent increased the amount of electrocyclization product. Plotting these product ratios versus Hammett σ_{para} constants produced a V-shaped curve (Figure 2). The shape of this curve indicates that either the mechanism or the identity of the turnover-limiting step is changing.[28] Alternatively, the shape of this curve could suggest the presence of radical intermediates in one of the product-determining steps.[29]

Table 3. Effect of Changing the Electronic Nature of the Rhodium *N*-Aryl Nitrene on the Reaction Outcome



entry	#	R	σ_{para}[a]	σ_{mb}[b]	$\sigma_{JJ}^{\bullet}$[b]	37:38	yield, %[c]
1	a	OMe	−0.27	−0.77	0.23	1:12	78
2	b	Me	−0.17	−0.29	0.15	1:7.2	79
3	c	H	0	0	0	1:5.8	82
4	d	F	0.06	−0.24	−0.02	1:5	92
5	e	Cl	0.23	0.11	0.22	1:6.6	76
6	f	OCF$_3$	0.35	–	–	1:9.5	80

[a] From ref 27. [b] From ref 34b. [c] As determined using ^{1}H NMR spectroscopy with CH$_2$Br$_2$ as an internal standard.

To investigate the latter possibility, these data were correlated to radical $\sigma^\bullet$ substituent constants. Toward this end, we examined the relationship between our relative rate data and Arnold's $\sigma_\alpha^\bullet$-,[30] Creary's $\sigma_C^\bullet$-,[31] and Jackson's $\sigma_J^\bullet$-constants.[32] Using these constants, no linear correlation was observed for styryl azide **33**.[33] In contrast, styryl azide **36**, which varied the electronic environment at the aryl azide piece, exhibited a linear relationship when its product ratio was plotted against Arnold's $\sigma_\alpha^\bullet$- or Creary's $\sigma_C^\bullet$-constants (Figure 3). We interpret this result to suggest the presence of a nitrogen-based radical in the product-determining step.

Next, we examined the relationship between our relative rate data and Jiang and Ji's radical σ_{mb} and $\sigma^\bullet_{JJ}$ substituent constants, which separate the polar (σ_{mb}) and spin ($\sigma^\bullet_{JJ}$) delocalization effects (Figure 4).[34] To accomplish this, we applied the σ_{mb} and

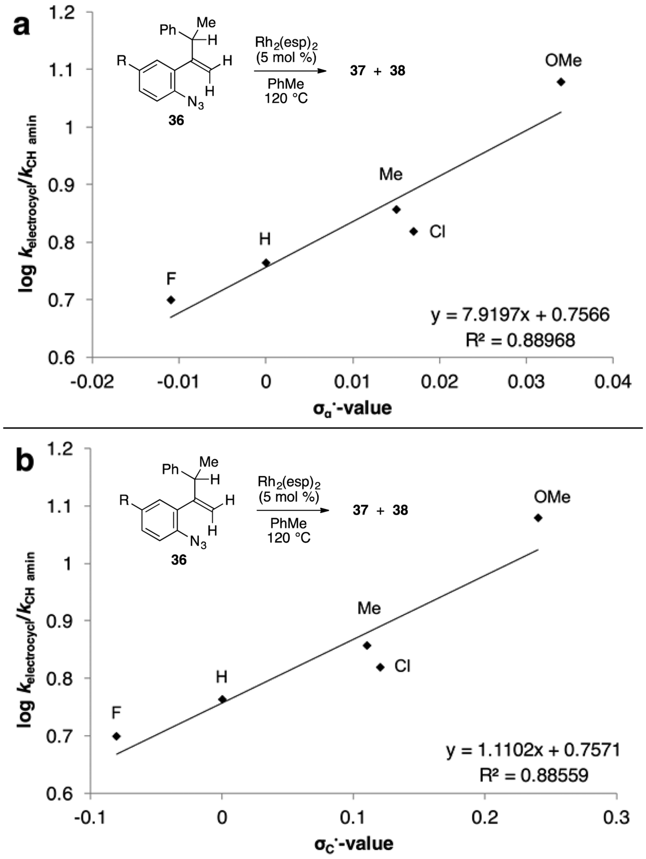


Figure 3. Correlation of heterocycle product ratios from styryl azide **36** with (a) Arnold's $\sigma_\alpha^\bullet$-constants and (b) Creary's $\sigma_C^\bullet$-constants.

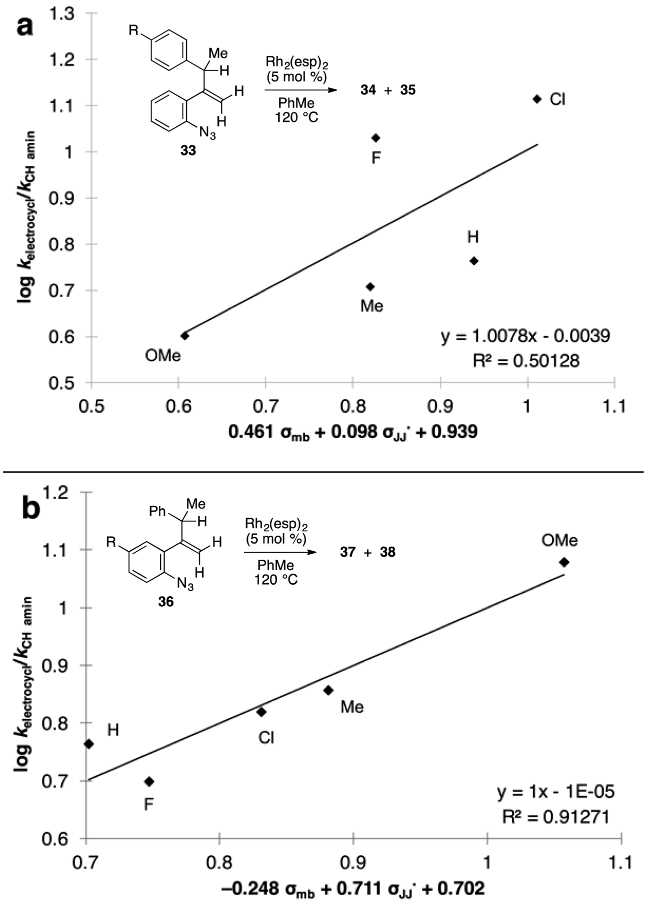
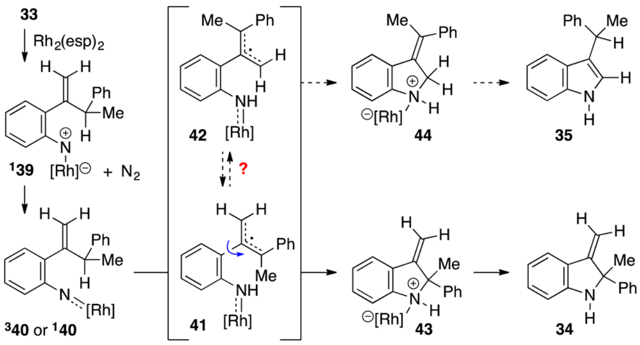


Figure 4. Correlation of heterocycle product ratios with Jiang and Ji's σ_{mb} and $\sigma_{JJ}^{\bullet}$ values. (a) Substituent effect observed at the allylic C−H reaction site; (b) substituent effect observed on the aryl azide.

$\sigma^{\bullet}_{JJ}$ substituent constants to our relative rate data ($\log k_{electrocycl}/k_{CHamin} = \rho_{mb}\sigma_{mb} + \rho_{JJ}^{\bullet}\sigma^{\bullet}_{JJ} + C$) for heterocycle formation from styryl azides **33** and **36**. For the reaction of styryl azides **33**, no linear correlation was observed using σ_{mb} and $\sigma^{\bullet}_{JJ}$ constants (Figure 4a). We interpret this result to indicate that the electronic effects observed during the product-determining step are entirely polar in nature and that no radical character is built up on the benzyl position during this step. In contrast, correlation was observed when the substituents were changed on styryl azide **36** to result in the straight line when $\log k_{rel} = -0.248\sigma_{mb} + 0.711\sigma^{\bullet}_{JJ} + 0.702$ (Figure 4b). The negative ρ_{mb} value is consistent with an electrophilic metal *N*-aryl nitrene catalytic intermediate, and the positive $\rho_{JJ}^{\bullet}$ suggests that the spin density is localized on the nitrogen atom. In both cases, the magnitude of $|\rho_{JJ}^{\bullet}/\rho_{mb}| > 1$ suggests that the spin delocalization effect is more important than the polar substituent effect.[34] Together with the lack of correlation observed with the benzyl series, these results suggest that H-atom abstraction by the rhodium *N*-aryl nitrene occurs though an early transition state in which little C−H bond homolysis has occurred. For these analyses, however, caution must be used in over-interpreting these ρ-values because these σ_{mb} and $\sigma^{\bullet}_{JJ}$ substituents were developed from benzyl carboradicals.[34]

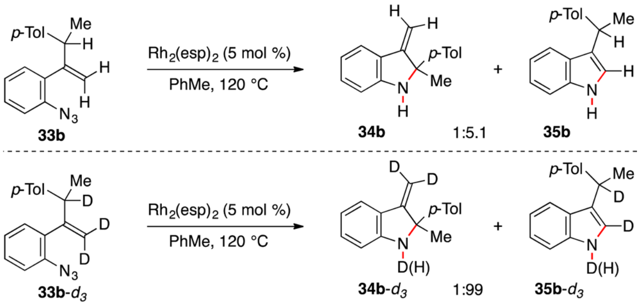
The correlation of our relative rate data to Jiang and Ji's polar and spin delocalization substituent constants suggests that indole **37** might also be formed through an H-atom abstraction−radical recombination mechanism instead of an electrocyclization (Scheme 5). In this potential mechanism, $Rh_2(II)$-catalyzed decomposition of styryl azide **33** forms rhodium nitrene **39**. While a singlet species will be first formed from loss of N_2,[35] our collaboration with Tantillo and co-workers revealed that a very small barrier separates it from the energetically preferred triplet rhodium nitrene **40**.[35] While this species was shown by the calculations to be inert toward cyclization with a β-substituted alkenyl group, we anticipated that, in systems that bear a weakened allylic C−H bond, hydrogen-atom abstraction could occur to form allyl radical **41**.[36] Radical recombination of **41** could form the minor product, 2*H*-indole **34**. Alternatively, bond rotation of **41** to **42** could occur to alleviate destabilizing steric interactions between the rhodium *N*-aryl nitrene and the phenyl- and methyl substituents of the allyl radical. Radical recombination forms 2*H*-indole **44**, which isomerizes to form the more stable indole **35**. While this mechanism might not be general, it could be considered a possibility in systems that contain weakened allylic C−H bonds.

Scheme 5. H-Atom Abstraction-Radical Recombination As a Potential Common Mechanism for 2*H*-Indole and Indole Formation



To investigate if both 2*H*-indole **34** and indole **35** are formed through a common allyl radical intermediate, the reactivity of styryl azide **33b**-d_3 was tested (Scheme 6). This labeled substrate was chosen because we anticipated that that the ratio of the *N*-heterocyclic products from **33b**-d_3 would be similar to the case of **33b**-d_0 since H-atom abstraction of the allylic C−H bond occurs for both and changing the bond strength should not affect the ratio if the product-determining step occurs afterward. In contrast, if the mechanism for indole **35** occurs instead through an electrocyclization of the rhodium *N*-aryl nitrene, then the formation of the 2*H*-indole product should be significantly diminished because electrocyclization avoids breaking the stronger C−D bond. Exposure of styryl azide

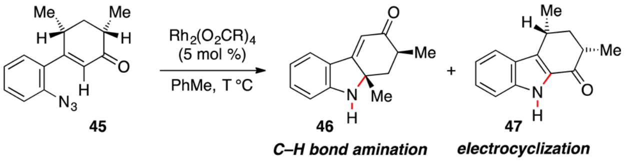
Scheme 6. Relationship between Isotopolog Identity and Ratio of 2*H*-Indole 34 and Indole 35 Using $Rh_2(esp)_2$ As the Catalyst



33-d_3 to reaction conditions formed >99% of indole **35b** with only a trace of 2*H*-indole **34b** observed. We interpret the increased amount of indole **35b**-d_3 to indicate that it is formed through an electrocyclization and not through a common allyl radical intermediate.

Investigation into Catalyst Control of Reaction Outcome. Because the more significant effect was observed when the electronic nature of the aryl azide moiety was modified, we anticipated that changing the identity of the catalyst might also control the ratio of electrocyclization to C−H bond amination (Table 4 and Figure 5). To investigate this assertion, styryl azide **45** was chosen because we anticipated that adding a methyl substituent to the allylic position of the *ortho*-enone substituent might make the C−H bond amination competitive with electrocyclization. In line with our hypothesis, exposure to $Rh_2(esp)_2$ afforded a 1:1.6 ratio of 2*H*-indole **46** and indole **47** (Table 4, entry 1). Reducing the temperature of the reaction affected neither the yield of heterocycle formation or the ratio of **46**:**47** (entry 2). The effect of the rhodium carboxylate catalyst in overturning the natural inclination of the free *N*-aryl nitrene is seen in entry 3: although the conversion at 120 °C is only 15%, the electrocyclization product, indole **47**, was observed as nearly the only product. Altering the identity of the carboxylate ligands had a measurable effect on the product ratio. Rhodium octanoate behaved similarly to $Rh_2(esp)_2$ albeit affording the heterocycle products in a slightly lower yield (entry 4). Changing the carboxylate ligand to a caprolactamate[37] resulted in selective formation (1:10) of the indole electrocyclization product (entry 5). The allylic C−H bond amination product **46** was favored slightly with chiral, nonracemic ligands *S*-DOSP and *S*-PTAD with a higher ratio of **46** obtained with the larger *S*-PTAD ligand (entries 6−9).[38,39] A slightly higher preference for **46** (3.9:1) was observed with $Rh_2(S\text{-PTAD})_4$, which could be increased to 4.8:1 if the reaction temperature was lowered to 90 °C. No further increase in the preference for sp^3-C−H bond was observed using $Rh_2(S\text{-PTAD})_4$ either if the dielectric of the solvent was changed through the addition of a tetraalkylammonium salt or if the solvent was changed to a chlorinated solvent. These results reveal that the reaction outcome of styryl azide **45** is affected by both the presence of the rhodium(II) catalyst and the identity of its ligands.

Table 4. Effect on the Reaction Outcome by Changing the Identity of the Rh_2(II)-Catalyst's Ligands



entry	$Rh_2(O_2CR)_4$	*T*, °C	**46**:**47**	yield, %[a]
1	$Rh_2(esp)_2$	120	1:1.6	91
2	$Rh_2(esp)_2$	110	1:1.7	90
3	none	120	1:16	15
4	$Rh_2(oct)_4$	110	1:2.1	78
5	$Rh_2(cap)_4$	100	1:10	73
6	$Rh_2(S\text{-DOSP})_4$	100	1.28:1	64[b]
7	$Rh_2(S\text{-PTAD})_4$	110	3.9:1	84
8	$Rh_2(S\text{-PTAD})_4$	100	4.4:1	85
9	$Rh_2(S\text{-PTAD})_4$	90	4.8:1	61[c]

[a] As determined by ^1H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] Only 84% conversion observed. [c] Only 72% conversion observed.

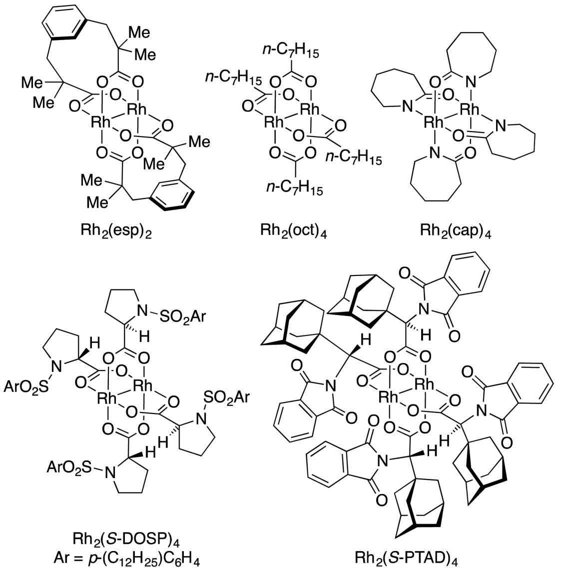
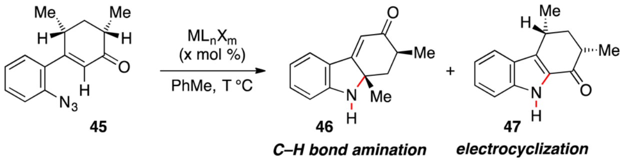


Figure 5. Structures of the Rh_2(II)-carboxylate catalysts investigated.

Table 5. Relationship between the Identity of the Metal of the *N*-Atom Transfer Catalyst and the Reaction Outcome



entry	ML_nX_m	mol %	*T*, °C	**46**:**47**	yield, %[a]
1	$Rh_2(esp)_2$	5	110	1:1.7	90
2	$[Ir(cod)(OMe)]_2$	5	110	0:100	88
3	$FeBr_2$	20	110	0:100	84
4	$FeBr_3$	20	110	0:100	41
5[b]	CoTPP	2	100	3.6:1	68
6[b]	CoOEP	2	100	8:1	18[c]
7[b]	Fe(TPP)Cl	2	100	13:1	52
8[b]	Fe(TPP)Cl	2	125	7.3:1	52
9[b]	Fe(TPFPP)Cl	2	110	3.3:1	72
10[b]	Fe(TOMePP)Cl	2	100	17:1	52
11[b]	Fe(OEP)Cl	2	100	60:1	77

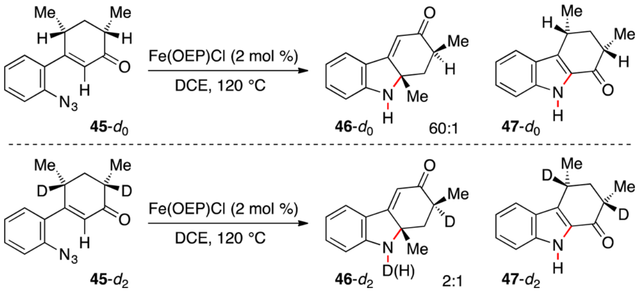
[a] As determined by ^1H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] Reaction performed in DCE with 100 wt % of 4 Å molecular sieves added. [c] Only 28% conversion observed.

Next, we examined changing the metal of the *N*-atom transfer catalyst (Table 5). We anticipated that a larger effect would be observed on the reaction outcome if the metal was involved in C−N bond formation or C−H bond cleavage. Consistent with this hypothesis, changing the identity of the metal had a significant effect on the preference for electrocyclization or C−H bond amination. While $Rh_2(esp)_2$ gave a mixture of 2*H*-indole **46** and indole **47** (entry 1), exposure of styryl azide **45** to 5 mol % of [Ir(cod) (OMe)]$_2$ produced only indole **47** (entry 2) in 88%. Indole **47** was also only observed using 20 mol % of ferrous or ferric chloride,[40] with a significantly higher yield observed with ferrous chloride (entries

3 and 4). In contrast, 2*H*-indole **46** was observed as the major product when cobalt or iron porphyrin complexes were employed as the catalyst (entries 5−11).[6,41] A higher preference for C−H bond amination was obtained with more electron-rich metal porphyrin catalysts. Because these complexes are well established to catalyze C- and N-atom transfer reactions through one-electron mechanisms,[42] we anticipated that higher activities might be observed with these catalysts if an H-atom abstraction−radical recombination was an accessible mechanism. In line with this assertion, we found that only 2 mol % of Co(TPP) at a lower temperature (100 °C) was required to produce **46** as the major product (entry 5). Changing the porphyrin ligand from tetraphenyl- to octaethylporphyrin improved the ratio of **46**:**47** from 3.6 to 8:1, but the conversion to the *N*-heterocycle plummeted to 28% (entry 6). A similar preference for 2*H*-indole formation was observed when the metal was changed from Co(II) to Fe(III). Iron tetraphenylporphyrin chloride catalyzed the formation of 2*H*-indole **46** with greater selectivity (13:1) in comparison to Co(TPP) albeit in slightly reduced yield (entry 7). In an attempt to improve the yield, the reaction temperature was increased from 100 to 125 °C. Unfortunately, the yield remained static and the selectivity for 2*H*-indole **46** was attenuated from 13:1 to 7.3:1 (entry 8). Next, we investigated changing the electronic nature of the iron porphyrin ligand (entries 9−11). We found that it played a critical role in promoting 2*H*-indole **46**: reduced selectivity (3.3:1) was observed using electron-poor iron perfluoroarylporphyrin, whereas the more electron-rich iron tetramethoxyarylporphyrin improved the selectivity for **46** to 17:1 (entries 9 and 10). The best selectivity for 2*H*-indole **46** formation was obtained using the electron-rich iron octaethylporphyrin chloride to afford **46** in a 60:1 ratio (entry 11). This survey revealed that the identity of the metal N-atom catalyst does control the reaction outcome. Indole **47** can be formed as the only product using 5 mol % of [Ir(cod)(OMe)]$_2$ or 20 mol % of simple FeBr$_2$, whereas 2 mol % of iron(III) octaethylporphyrin chloride leads to selective 2*H*-indole **46** formation with only a trace of indole **47** observed.

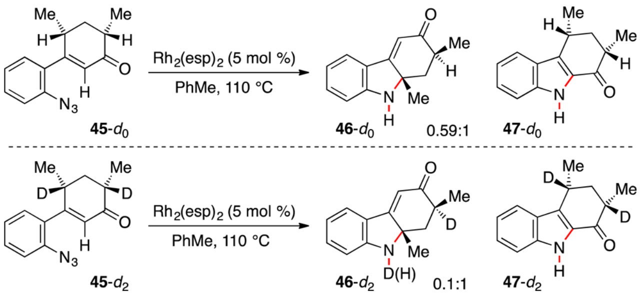
To gain further insight into factors that affect the reaction outcome using iron octaethylporphyrin chloride as the catalyst, styryl azide **45**-d_2 was examined (Scheme 7). We anticipated that the product ratio from **45**-d_2 would be the same as in the case of **45**-d_0 if both 2*H*-indole **46** and indole **47** were formed through a common allyl radical intermediate. Similar to our investigation of aryl azide **33b**-d_3 using Rh$_2$(esp)$_2$, exposure of **45**-d_2 to reaction conditions resulted in a significant reduction of the ratio of 2*H*-indole **46** to indole **47**. As before, we interpret this result to indicate that indole is formed through an electrocyclization process while 2*H*-indole is formed through an H-atom abstraction radical−recombination mechanism. The value of the primary kinetic isotope effect (approximately 30)[43] is significantly larger than the classical value for H-atom transfer (6.5)[44] and suggests that tunneling is occurring.

Scheme 7. Relationship between Isotopolog Identity and Ratio of 2*H*-Indole 46 and Indole 47 Using Fe(OEP)Cl as the Catalyst

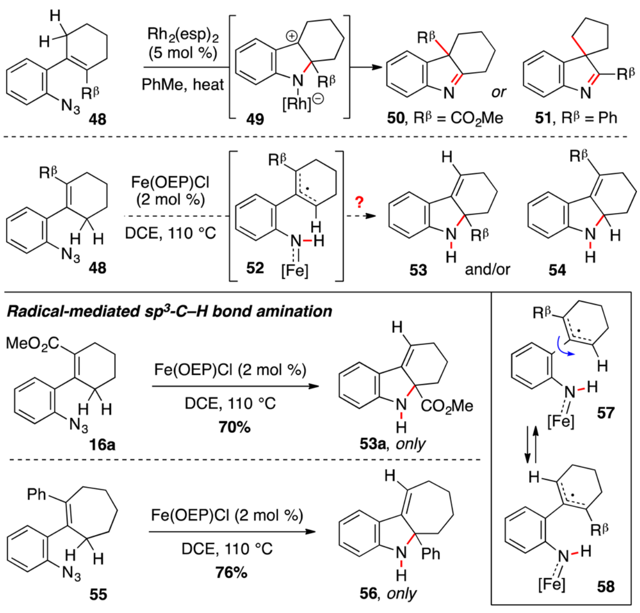


The reactivity of the styryl azide **45**-d_2 was also investigated using Rh$_2$(esp)$_2$ as catalyst to examine if a similar change in the ratio of product 2*H*-indole **46** and indole **47** was observed (Scheme 8). A 1:1.63 ratio of 2*H*-indole **46** to indole **47** was obtained from stryryl azide **45**-d_0 using Rh$_2$(esp)$_2$. Similar to the use of Fe(OEP)Cl as catalyst, significantly less allylic C−H bond amination was observed when **45**-d_2 was submitted to Rh$_2$(esp)$_2$ producing a 1:10 ratio of **46**-d_2 and **47**-d_2. The exhibited primary kinetic isotope effect, however, is much smaller (approximately 6)[43] to suggest that tunneling is not occurring. We interpret these data in support of two separate mechanisms: allylic C−H bond amination produces 2*H*-indole **46** while an electrocyclization−migration sequence affords indole **47**.

Scheme 8. Comparison of Ratio of 2*H*-Indole 46 and Indole 47 Using Rh$_2$(esp)$_2$ as the Catalyst



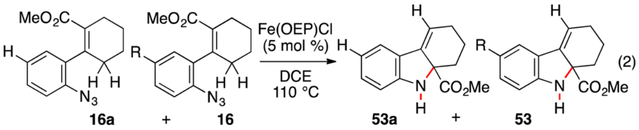
Scheme 9. Reversing the Inherent Chemoselectivity of a Styryl Azide by Catalyst



Finally, the generality for iron octaethylporphyrin chloride to change the reaction outcome in β-substituted styryl azides was investigated (Scheme 9). Upon exposure to a Rh$_2$(II)-

carboxylate catalyst, these substrates can be transformed into 3*H*-indole **50** or spirocycle **51** through a [1,2] migration of one of the β-substituents in the electrocyclization product **49**. We anticipated if the reaction was changed from a two-electron- to a one-electron process, however, that a different *N*-heterocycle would be accessed by changing the identity of the reactive intermediate. Instead of triggering a migration or ring contraction via the electrocyclization product cation **49**, H-atom abstraction of the iron *N*-aryl nitrene would produce allyl radical **52**.[45] This radical intermediate could be captured by the nitrogen-centered radical to produce 2*H*-*N*-heterocycle **53** or **54**. To test this, styryl azides **16a** and **55** were exposed to 2 mol % of Fe(OEP)Cl and 2*H*-indoles **53a** and **56** were produced as the only products. The regioselectivity of C−N bond formation suggests that allyl radical **57** is sufficiently long-lived for bond rotation to occur before radical recombination between the more substituted side and the nitrogen-centered radical. Consistent with our hypothesis that radical intermediates are generated, the addition of the radical inhibitor TEMPO or 1,4-cyclohexadiene blocked heterocycle formation.

To further explore the reactivity of the catalytic intermediates generated from styryl azide **16a** and Fe(OEP)Cl, a series of competition experiments were performed using *para*-substituted styryl azides **16** (eq 2). We found that the presence of either an electron-donating or -withdrawing R-substituent increased the rate of the reaction. The relative rates of the starting styryl azides **16** were analyzed using the Hammett equation using σ_{para} values to produce a V-shaped curve suggesting the formation of radical intermediates (Figure 6a). Next, our relative rate data were plotted using Jiang and Ji's radical σ_{mb} and $\sigma^{\bullet}_{JJ}$ substituent constants (Figure 6b).[34] The best linear correlation was obtained using log $k_{rel} = -0.483\sigma_{mb} + 1.13\sigma^{\bullet}_{JJ} + 0.05$. Similar to data observed from $Rh_2(esp)_2$ and styryl azide **36**, a negative ρ_{mb} value and a positive $\rho_{JJ}{}^{\bullet}$ were obtained to suggest that the spin density is localized on an electrophilic nitrogen atom. In comparison to our earlier Rh_2(II)-study of styryl azide **36**, a similar absolute value of $|\rho_{JJ}{}^{\bullet}/\rho_{mb}|$ (2.33 versus 2.87) was obtained to suggest that the spin delocalization effect is also important with this substrate series using Fe(OEP)Cl as the catalyst. These correlations suggest that radical intermediates are formed in this Fe-catalyzed reaction.



(2)

CONCLUSIONS

Our studies provide mechanistic insight into the controlling elements of the reactivity of metal *N*-aryl nitrene. Electrocyclization is favored for mono-β-substituted and sterically noncongested styryl azides, whereas sp^3-C−H bond amination is preferred when weakened allylic reaction centers are present. In the presence of a sufficiently activating amino- or carbonyl β-substituent, tertiary allylic C−H bond amination will occur even if the π-system is sterically noncongested. Our results show that the site selectivity of metal *N*-aryl nitrenes can be controlled by the choice of catalyst: Ir(I)-alkene complexes trigger electrocyclization processes while Fe(III) porphyrin complexes catalyze sp^3-C−H bond amination in substrates where Rh_2(II) carboxylate catalysts provide both products.

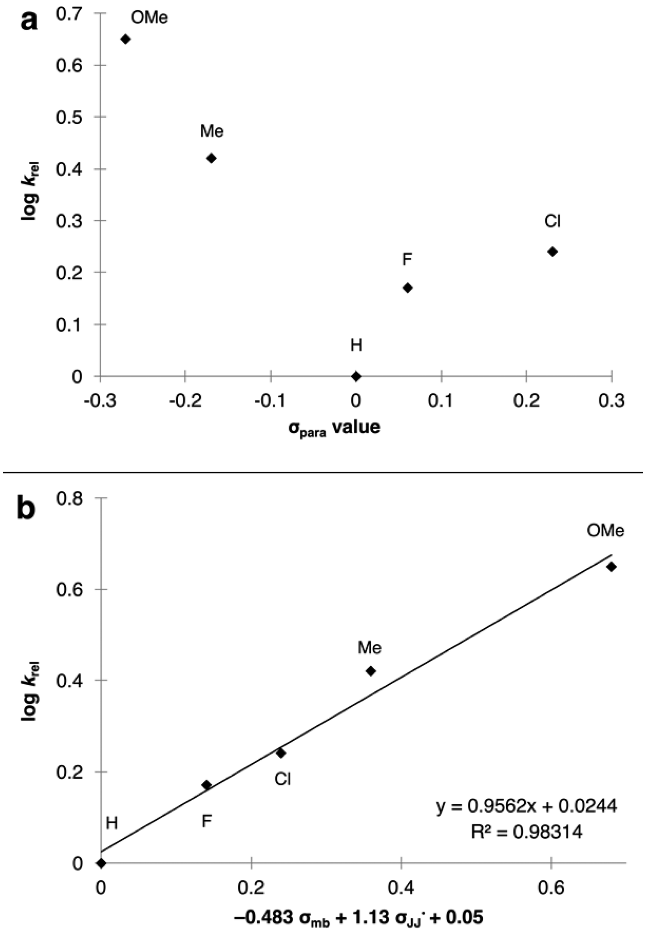


Figure 6. Correlation of relative rates between substituted styryl azides **16** and **16a** with (a) σ_{para}-constants and (b) Jiang and Ji's σ_{mb} and $\sigma_{JJ}{}^{\bullet}$ values.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07026.

Experimental procedures, spectroscopic and analytical data for the products (PDF)

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Notes

The authors declare no competing financial interest.

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