Organic LETTERS

Letter

pubs.acs.org/OrgLett

Achieving Site Selectivity in Metal-Catalyzed Electron-Rich Carbene Transfer Reactions from *N*-Tosylhydrazones

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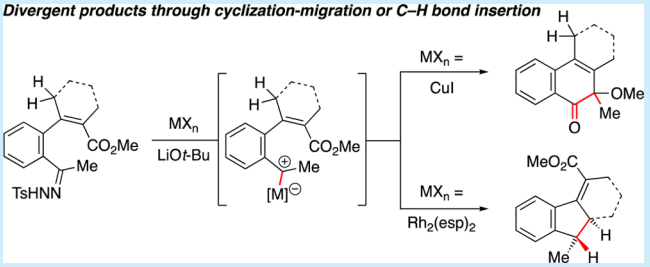
Supporting Information

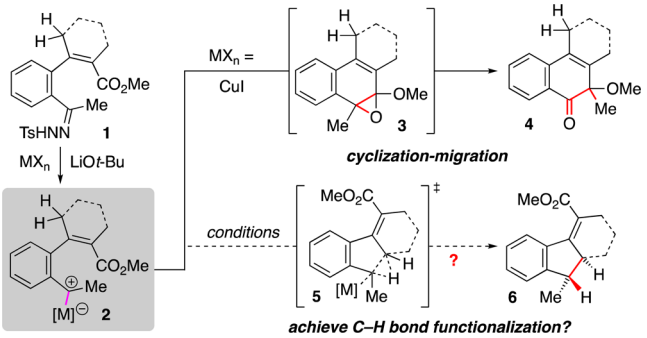
ABSTRACT: Catalyst control of the site-selectivity of electron-rich alkyl, aryl disubstituted carbenes generated in situ from *o*-alkenyl-substituted *N*-tosylhydrazones was achieved in this study. Exposure of these substrates to copper iodide triggered the formation of α-alkoxy 2*H*-naphthalenones. This investigation established that changing the catalyst to a rhodium(II) carboxylate turned off cyclization and migration of the electron-rich metal carbene with the β-carboxylate and turned on allylic C−H bond functionalization to diastereoselectively afford 1*H*-indenes. Examination of the scope of this reaction revealed that ethereal, aminomethylene, and unactivated 2° C−H bonds could be functionalized.



The ability of site-selective transition-metal-catalyzed reactions to produce divergent products from a single reactant by changing the identity of the catalyst continues to inspire significant research interest.[1,2] Catalyst-dependent transformations of carbenes derived from α-diazocarboxylates have emerged to control whether the electron-deficient metal carbene participates in a cycloaddition, cyclopropanation, or C−H bond insertion reaction.[2f,3] In contrast, controlling the chemoselectivity of electron-rich metal carbenes remains nascent.[4,5] The generation of electron-rich alkyl-substituted carbenes introduces the potential for β-hydride elimination,[6] which have been leveraged in cross-coupling reactions and sigmatropic rearrangements.[7,8] Accordingly, the use of these in sp^3-C−H bond functionalization reactions remains rare.[9,10] As part of our interest of metal divalent catalytic intermediates,[11] we investigated the reactivity of *o*-alkenyl *N*-tosylhydrazone **1** to determine if metal aryl carbene **2** could participate in domino cyclization−migration reactions and found that copper iodide triggered the formation of α-methoxy 2*H*-naphthalene **4** through the rearrangement of epoxide **3** (Scheme 1).[12] At the conclusion of this study, we were curious if changing the identity of the catalyst could trigger sp^3-C−H bond functionalization to construct 1*H*-indenes from the same *N*-tosylhydrazone starting materials.

Our investigation into the catalyst that selects for allylic sp^3-C−H bond insertion instead of cyclization−migration of the electron-rich alkyl, aryl disubstituted carbene was initiated using *o*-alkenyl-substituted *N*-tosylhydrazone **9a** (Table 1). This substrate was chosen to determine the optimal conditions because hydrazones have been established as safe sources of alkyl diazo compounds through a Bamford−Stevens−Shapiro reaction,[4a,13] and **9a** is readily available from a Suzuki−Miyaura

Scheme 1. Potential for Divergent Reactivity of Electron-Rich Metal Alkyl, Aryl Carbene Catalytic Intermediates

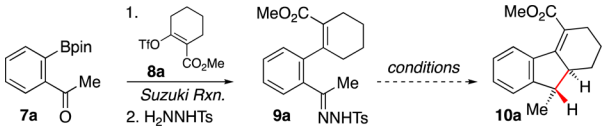


cross-coupling reaction between arylboronic acid **7a** and vinyl triflate **8a**. Because of their ability to trigger C−H bond functionalizations of metal carbenes,[14] we decided to first examine rhodium(II) carboxylates. While exposure of **9a** to 5 mol % of $Rh_2(OAc)_4$ and LiO-*t*-Bu (1.1 equiv) afforded only decomposition, C−H bond functionalization was observed when the identity of the carboxylate ligand was changed to triphenylacetate or pivaloate (entries 2−4). The yield of 1*H*-indene **10a** was increased to 44% using 5 mol % of $Rh_2(esp)_2$ as the catalyst.[15] Although varying the reaction temperature or the alkoxide base did not improve the reaction outcome (entries 6−8), the identity of the solvent was found to play a critical role. A screen of chlorinated, polar aprotic, and ethereal solvents revealed that the best yield and stereoselectivity

Received: June 5, 2017

DOI: 10.1021/acs.orglett.7b01694
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of the C−H Bond Functionalization Reaction



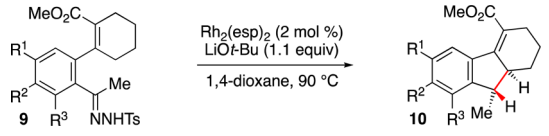
entry	catalyst (amt (mol %))	solvent	base[a]	temp (°C)	yield (%)[b]
1		PhMe	LiO-*t*-Bu	90	dec
2	$Rh_2(OAc)_4$ (5)	PhMe	LiO-*t*-Bu	90	dec
3	$Rh_2(tpa)_4$ (5)	PhMe	LiO-*t*-Bu	90	14
4	$Rh_2(Piv)_4$ (5)	PhMe	LiO-*t*-Bu	90	25
5	$Rh_2(esp)_2$ (5)	PhMe	LiO-*t*-Bu	90	44
6	$Rh_2(esp)_2$ (5)	PhMe	LiO-*t*-Bu	120	40
7	$Rh_2(esp)_2$ (5)	PhMe	LiOMe	90	30
8	$Rh_2(esp)_2$ (5)	PhMe	LHMDS	90	dec
9	$Rh_2(esp)_2$ (5)	DCE	LiO-*t*-Bu	90	47
10	$Rh_2(esp)_2$ (5)	chloroform	LiO-*t*-Bu	90	71
11	$Rh_2(esp)_2$ (5)	MeCN	LiO-*t*-Bu	90	67
12	$Rh_2(esp)_2$ (5)	1,4-dioxane	LiO-*t*-Bu	90	99[c]
13	$Rh_2(esp)_2$ (2)	1,4-dioxane	LiO-*t*-Bu	90	97[c]

[a]1.1 equiv of base used. [b]As determined using ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard. [c]Product isolated as a 15:1 mixture of diastereomers.

occurred in 1,4-dioxane (entries 9−12). Using this solvent, the catalyst loading could be reduced to 2 mol % and produce 1*H*-indene **10a** in 97% yield as a 15:1 mixture of diastereomers.[16]

Next, the scope and limitations of this reaction were examined using *N*-tosylhydrazones derived from ortho-substituted aryl ketones (Table 2). First, the dependence of the reaction outcome on the electronic nature of **9** was determined by changing the identity of the R^1 and R^2 substituents (entries 1−10). The C−H bond functionalization reaction was found to be insensitive to the electron-withdrawing effect of the R^1 substituent (entries 1−6). In contrast to the high yields and diastereoselectivities obtained from **9a−f**,

Table 2. Exploration of the Scope and Limitations of the Aryl Hydrazone Moiety



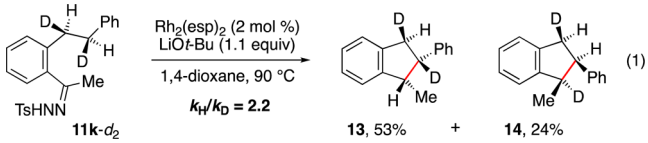
entry	compd	R^1	R^2	R^3	yield (%)[a]	dr[b]
1	**a**	H	H	H	93 (84)[c]	15:1
2	**b**	CF_3	H	H	97	17:1
3[d]	**c**	Cl	H	H	88	13:1
4	**d**	F	H	H	96	13:1
5	**e**	Ph	H	H	86	20:1
6	**f**	Me	H	H	90	17:1
7	**g**	MeO	H	H	20	13:1
8	**h**	H	Cl	H	100	17:1
9	**i**	H	Me	H	100	20:1
10	**j**	H	MeO	H	96	20:1
11	**k**	H	H	F	96	13:1
12	**l**	H	H	MeO	dec	

[a]Isolated yield of **10** after neutral alumina chromatography. [b]dr determined by ^{1}H NMR spectroscopy. [c]1 mmol scale. [d]5 mol % of $Rh_2(esp)_2$ used.

exposure of hydrazone **9g** bearing an R^1 methoxy group to the reaction conditions resulted in a significantly reduced yield of 1*H*-indene **10g** (entry 7). This electron-releasing substituent appears to attenuate the electrophilicity of the carbene intermediate to react with the allylic C−H bond. In contrast, the electronic identity of the R^2 substituent did not affect the yield or the diastereselectivity of 1*H*-indenes **10h−j** (entries 8−10). The reaction proved to be sensitive to the identity of the R^3 substituent (entries 11 and 12). While a fluorine was tolerated, only decomposition was observed when an electron-donating methoxy substituent was present.

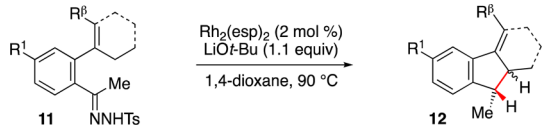
The identity of the ortho substituent was varied to further investigate the scope of this reaction (Table 3). We found that the R^β group could be changed from a carboxylate to a phenyl without adversely affecting the yield of 1*H*-indene **12** formation, irrespective of the electronic nature of the aryl ring (entries 1−3). The increased yield of **12c** in comparison to **10g** suggests that reducing the acidity of the C−H reaction center[17] or weakening the strength of its bond has a positive effect.[18] Next, the effect of changing the ring size of the *o*-cycloalkenyl substituent on the reaction outcome was surveyed (entries 4 and 5). While *o*-cyclopentyl hydrazone **11d** was smoothly transformed into 1*H*-indene **12d**, exposure of *o*-cycloheptenyl **11e** resulted in a precipitous drop in the stereoselectivity of the process. Substrates bearing a *β*-methyl substituent or an ortho-unsaturated cyclic ether could be smoothly and stereoselectively transformed into 1*H*-indenes **12f,g** (entries 6 and 7). The site selectivity for the allylic C−H bond could be overridden by conformational restraints: exposure of *o*-norbornene **11h** to the reaction conditions resulted in functionalization of the vinyl sp^2-C−H bond to produce **12h** as a single diastereomer (entry 8). Our reaction was also found to effectively functionalize other activated C−H bonds. Substrates bearing ethereal, aminomethylene, or benzyl C−H reaction centers were transformed into **12i−k** (entries 9−11). Quantitative formation of indane **12k** as a single diastereomer highlights the synthetic efficiency of our reaction (entry 11). The success of these substrates encouraged us to examine if functionalization of unactivated sp^3-C−H bonds could be achieved. Exposure of *o*-cyclohexyl *N*-tosylhydrazone **11l** to the optimal reaction conditions produced indane **12l** in good yield, albeit as a 3:1 mixture of diastereomers (entry 12).[19] To determine if the diastereoselectivity of the C−H bond functionalization could be improved if the size of the alkyl group on hydrazone was increased from methyl to isopropyl, substrate **11m** was examined (entry 13). Unfortunately, only *β*-hydride elimination was observed. Finally, the site selectivity between secondary and tertiary sp^3-C−H bonds was investigated with *N*-tosylhydrazone **11n** (entry 14). We found that both positions were reactive, but the reaction occurred primarily at the tertiary C−H bond to produce indane **12n** as a single diastereomer (54%) with the secondary C−H bond functionalization indane formed as a 3:1 mixture of diastereomers in 21% yield.

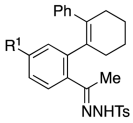
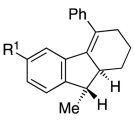
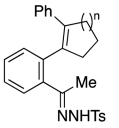
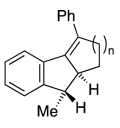
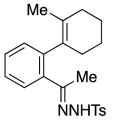
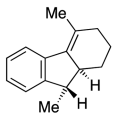
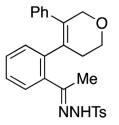
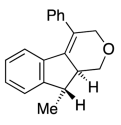
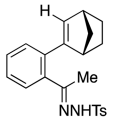
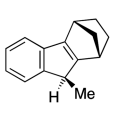
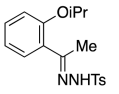
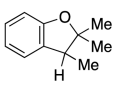
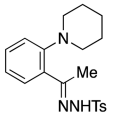
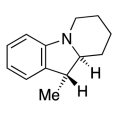
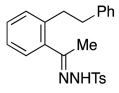
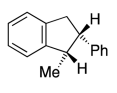
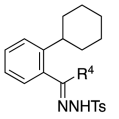
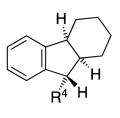
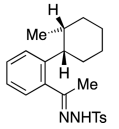
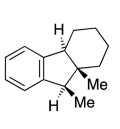
A deuterium labeling experiment was performed to provide insight into the mechanism of the C−H bond functionalization step of the catalytic cycle (eq 1). We anticipated that the



DOI: 10.1021/acs.orglett.7b01694
Org. Lett. XXXX, XXX, XXX−XXX

Table 3. Investigation of the Effect of Changing the Ortho Substituent



entry	#	hydrazone **11**	indene **12**	%, yield[a]	dr[b]
1	**a**			R^1 = H, 96	20:1
2	**b**			R^1 = Cl, 100	6:1
3	**c**			R^1 = OMe, 90	10:1
4	**d**			n = 1, 70	20:1
5	**e**			n = 3, 100	1.1:1
6	**f**			100	13:1
7	**g**			80	>95:5
8	**h**			100	>95:5
9	**i**			76[c]	...
10	**j**			64	2:1
11	**k**			100	>95:5
12	**l**			R^4 = Me, 86	3:1
13	**m**			R^4 = iPr, 0[d]	...
14	**n**			54[e]	>95:5

[a]Isolated yield of **10** after neutral alumina chromatography. [b]dr determined by ^{1}H NMR spectroscopy. [c]As determined using ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard. [d]93% of the β-hydride elimination product obtained. [e]21% of the 2° C−H bond functionalization product formed as a 3:1 mixture of diastereomers.

number of diastereomers formed from *N*-tosylhydrazone **11k**-d_2 would reveal if C−H bond functionalization was stepwise or concerted. If the reaction was concerted, then insertion into the β-C−H or β-C−D bond would produce indanes **13** and **14**. In contrast, if the C−H bond functionalization occurred through an H atom abstraction followed by radical recombination or if a carbocation was formed, then the stereochemical information embedded at the β carbon would be lost and four products would be formed. Alternatively, if the kinetic isotope effect was very large, then two diastereomers of **13** would be observed. In support of a concerted insertion of the electron-rich metal carbene into the C−H bond, exposure of **11k**-d_2 to the reaction conditions produced only indanes **13** and **14**. Our observed intramolecular kinetic isotope effect of 2.2 is similar to the k_H/k_D values of 2.0 and 1.9 reported for the intermolecular insertion of electron-poor carboxylic ester- and imine-substituted rhodium(II) carbenes.[20]

In conclusion, we have shown that the reactivity of electron-rich metal alkyl, aryl disubstituted carbenes can be controlled by the identity of the metal. While copper aryl, alkyl carbenes react with the *o*-alkenyl substituent through a cyclization−migration pathway to afford α-alkoxy 2*H*-naphthalenones, rhodium(II) carboxylates trigger a stereoselective allylic C−H bond functionalization to produce 1*H*-indenes. This C−H bond functionalization is not limited to allylic C−H bonds, but ethereal, aminomethylene, and even unactivated 2° sp^3-C−H bonds can be functionalized.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01694.

Experimental procedures and analytical data (PDF)
X-ray data for the allylic alcohol derived from **10a** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Science Foundation (CHE-1564959), the University of Illinois at Chicago, Office of the Vice-Chancellor of Research, Huaqiao University, Xiamen and the Fujian Hundred Talents Plan for their generous financial support. We thank Mr. Furong Sun (UIUC) for high-resolution mass spectrometry data and Mr. Bryant T. Thurman for helping in the synthesis of *N*-tosylhydrazone **9a** for the 1 mmol scale reaction.

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DOI: 10.1021/acs.orglett.7b01694
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DOI: 10.1021/acs.orglett.7b01694
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