JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Direct Transformation of Terminal Alkynes to Branched Allylic Sulfones

Kun Xu, Vahid Khakyzadeh, Timm Bury, and Bernhard Breit*

Institut für Organische Chemie, Albert-Ludwigs-Universität Freiburg, Albertstrasse 21, 79104 Freiburg i. Brsg., Germany

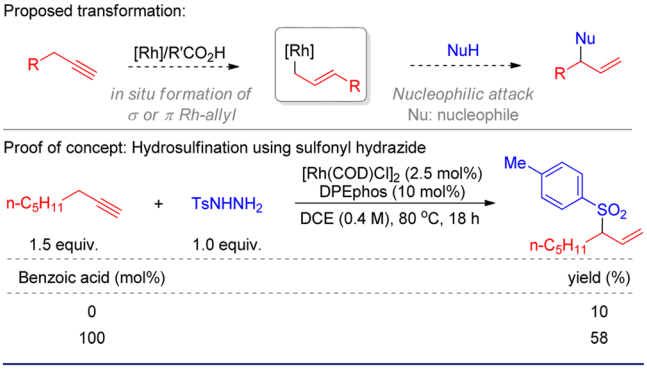
Supporting Information

ABSTRACT: A new strategy for the transformation of terminal alkynes to branched allylic sulfones was developed. Using a Rh(I)/DPEphos/benzoic acid catalyst system, terminal alkynes react with sulfonyl hydrazides to produce branched allylic sulfones with good to excellent yields and selectivities in general.

Transformation of simple and readily accessible starting materials to branched allylic derivatives is an important topic in organic synthesis because of the versatility of the allylic moiety for further elaboration, and the stereogenic center for asymmetric synthesis.[1] In recent decades, significant progress toward this goal has been achieved, in particular with allylic substitution[1] and allylic C−H oxidation[2] chemistry. However, these methods require preinstallation of a leaving group or stoichiometric amounts of an oxidant, respectively. More recently, our group has discovered rhodium catalyzed coupling of allenes with pronucleophiles[3] toward the synthesis of branched allylic products.[4] Alternatively, the easily accessible terminal alkynes[5] can couple with carboxylic acids in the presence of a suitable rhodium catalyst to form the corresponding branched allylic esters.[6a,b] Unfortunately, replacement of carboxylic acids with other pronucleophiles to provide new branched allylic derivatives only led to no reaction or traces of product after intensive efforts, possibly due to the difficulty of the alkyne to allene isomerization or the rhodium-allyl formation.[6c]

Mechanistic investigations on the coupling of carboxylic acids with terminal alkynes indicated that the reaction involves a rhodium/carboxylic acid catalyzed isomerization of an alkyne to an allene, followed by formation of a Rh-allyl species, which is the turnover determining intermediate of the catalytic cycle.[6c] We wondered whether such an *in situ* formed σ or π rhodium-allyl species could be attacked by an external nucleophile to produce the corresponding branched allylic derivative (Scheme 1). To this end, sulfonyl hydrazides were chosen as the benchmark pronucleophile based on the following reasons: (1) the high nucleophilicity of an *in situ* generated sulfonyl anion[7] may facilitate the attack to rhodium-allyl intermediates;[8] (2) sulfonyl hydrazides are easily accessible;[9] (3) sulfones, particularly allylic sulfones, are useful building blocks in organic synthesis[10] and pharmaceuticals.[11] Sulfone derivatives bearing an α-chiral center are an important class of compounds in biological research. For example, Dorzolamide, Tazobactam, and Dalfopristin are prescription drugs used as an antiglaucoma agent, for antibiotic treatments, and as an anti-infective agent,

Scheme 1. Transformation of Terminal Alkynes to Branched Allylic Sulfones



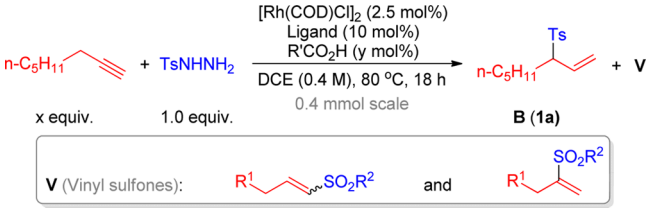
respectively.[11e−g] Herein, we report a rhodium catalyzed hydrosulfination of terminal alkynes with sulfonyl hydrazides as an efficient method for the synthesis of branched allylic sulfones.[7b,12]

To test our hypothesis, the reaction of *p*-toluenesulfonyl hydrazide (1.0 equiv) and 1-octyne (1.5 equiv) with $[Rh(COD)Cl]_2$ (2.5 mol %) and (oxydi-2,1-phenylene)bis(diphenylphosphine) (DPEphos, 10 mol %) in 1,2-dichloroethane (DCE, 0.4 M) was heated at 80 °C for 18 h with 1.0 equiv of benzoic acid. To our delight, the reaction gave a promising 58% NMR yield of the branched allylic sulfone (B), albeit a trace amount of vinyl sulfones (V) were formed (B/V = 92/8, Table 1, entry 1). Notably, the reaction without benzoic acid gave only 10% of the desired product (Scheme 1). Encouraged by this result, we then checked different parameters of the reaction conditions. Bidentate phosphine ligands with different bite angles were investigated, yet DPEphos was found to be the most efficient in terms of reactivity and selectivity (Table 1, entries 2−5). The amount of benzoic acid is crucial for the reaction, as lower benzoic acid loadings led to reduced yields and lower selectivities (Table 1, entries 6−7). The branched allylic product (**1a**) was isolated with a 92% yield when a higher alkyne loading (2.5 equiv) was used (Table 1, entry 8). Other carboxylic acids with different pK_a values proved to be less efficient than benzoic acid (Table 1, entries 9−10). Control experiments indicated that both the rhodium precursor and the ligand were necessary for the reaction to proceed.[13]

Received: September 11, 2014
Published: November 3, 2014

   dx.doi.org/10.1021/ja509383r | J. Am. Chem. Soc. 2014, 136, 16124−16127

Table 1. Optimization of Rh-Catalyzed Hydrosulfination



entry	ligand	*x*	R′	*y*	yield/%[a]	B/V[b]
1	DPEphos	1.5	Ph	100	58	92/8
2	dppb	1.5	Ph	100	12	93/7
3	dppp	1.5	Ph	100	23	97/3
4	dppf	1.5	Ph	100	47	92/8
5	*rac*-binap	1.5	Ph	100	35	63/37
6	DPEphos	1.5	Ph	20	47	80/20
7	DPEphos	1.5	Ph	50	64	91/9
8	DPEphos	2.5	Ph	50	(92)[c]	93/7
9	DPEphos	2.5	CH_3	50	35	58/42
10	DPEphos	2.5	$^{p}CF_3Ph$	50	54	89/11

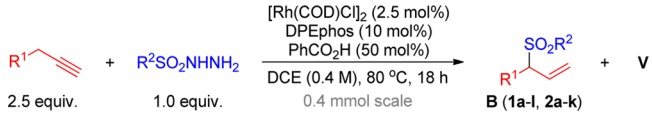
[a]^{1}H NMR yield of the branched product in the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [b]Ratio of B/V was determined by ^{1}H NMR of the crude reaction mixture. [c]Isolated yield of the branched product. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, cod = 1,5-cyclooctadiene, dppb = 1,4-bis(diphenylphosphino)butane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, dppp = 1,3-bis(diphenylphosphino)propane.

With the optimized conditions in hand, we then evaluated the scope of the reaction. Various terminal alkynes were coupled with *p*-toluenesulfonyl hydrazide to give the corresponding branched allylic sulfones with good to excellent yields and selectivities in most cases (Table 2, **1a**–**l**). Several functional groups (cyano, ester, protected amide, and even free hydroxyl) were well tolerated (**1h**–**l**), and both aliphatic and aromatic substituted terminal alkynes were compatible (**1a**–**g**), although sterically hindered terminal alkynes gave lower yields and selectivities (**1c**–**d**). A series of sulfonyl hydrazides reacted with 1-octyne to give the corresponding branched allylic sulfones (Table 2, **2a**–**k**). Diversely substituted aromatic sulfonyl hydrazides were suitable substrates (**2a**–**i**). Benzyl and alkyl substituted sulfonyl hydrazides can also be transferred to the valuable branched allylic sulfones (**2j**–**k**).

To probe the reaction mechanism, control experiments of $TsNHNH_2$ (**N1**) and 4-methylbenzenesulfinic acid (**N2**) with a branched benzoic ester (**E1**), allene (**E2**), and alkyne (**E3**) were performed (Table 3). Benzoic acid had little impact on the reactivity of the ester (**E1**) with $TsNHNH_2$ (Table 3, entries 1–2). This suggests that the ester (**E1**) can undergo oxidative addition with rhodium(I) to form a rhodium-allyl species followed by nucleophilic attack under both neutral and acidic conditions. The reaction of the allene (**E2**) with $TsNHNH_2$ was accelerated in the presence of 50% benzoic acid (Table 3, entries 3–4), which indicates that benzoic acid is essential for the formation of rhodium-allyl species.

The reactions of 4-methylbenzenesulfinic acid (**N2**) with the ester (**E1**) gave high yields of the desired product (Table 3, entries 5–6). However, the reactions of **N2** with the allene (**E2**) and alkyne (**E3**) only led to traces of or no product formation (Table 3, entries 7–10). We suspect that the low reactivities of the allene and alkyne with **N2** arise from the relatively higher acidity of **N2** ($pK_a \approx 2.1$) compared to benzoic aicd ($pK_a = 4.2$). The presence of large amounts of acidic **N2** would suppress the isomerization of the alkyne, as well as transformation of the allene to a rhodium-allyl species.

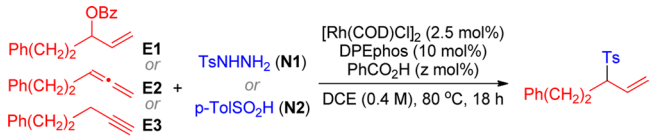
Table 2. Scope of Rh-Catalyzed Hydrosulfination



entry	R^1	R^2	yield/%[a]	B/V[b]
1	n-C_5H_{11}	*p*-Tol	92 (**1a**)	93/7
2	n-C_4H_9	*p*-Tol	82 (**1b**)	94/6
3	$(CH_3)_2CH$	*p*-Tol	63 (**1c**)[c]	79/21
4	cyclopentyl	*p*-Tol	61 (**1d**)[c]	82/18
5	$Ph(CH_2)_2$	*p*-Tol	90 (**1e**)	93/7
6	$PhCH_2$	*p*-Tol	83 (**1f**)	93/7
7	Ph	*p*-Tol	70 (**1g**)[c]	82/18
8	$NC(CH_2)_2$	*p*-Tol	78 (**1h**)	82/18
9	$CH_3O_2C(CH_2)_2$	*p*-Tol	88 (**1i**)	89/11
10	$PhthN(CH_2)_2$	*p*-Tol	74 (**1j**)	79/21
11	$TBSO(CH_2)_2$	*p*-Tol	70 (**1k**)	95/5
12	$HO(CH_2)_8$	*p*-Tol	79 (**1l**)	87/13
13	n-C_5H_{11}	Ph	86 (**2a**)	93/7
14	n-C_5H_{11}	1-naphthyl	80 (**2b**)	92/8
15	n-C_5H_{11}	2-naphthyl	90 (**2c**)	95/5
16	n-C_5H_{11}	2-Me-Ph	86 (**2d**)	98/2
17	n-C_5H_{11}	3-Me-Ph	59 (**2e**)	95/5
18	n-C_5H_{11}	4-F-Ph	78 (**2f**)	92/8
19	n-C_5H_{11}	4-Cl-Ph	75 (**2g**)	94/6
20	n-C_5H_{11}	4-Br-Ph	62 (**2h**)	95/5
21	n-C_5H_{11}	4-MeO-Ph	78 (**2i**)	90/10
22	n-C_5H_{11}	$PhCH_2$	71 (**2j**)	91/9
23	n-C_5H_{11}	$CH_3(CH_2)_2$	74 (**2k**)[c]	86/14

[a]Isolated yield of branched products. [b]Ratio of B/V was determined by ^{1}H NMR of the crude reaction mixture. [c]$[RhCODCl]_2$ (5.0 mol %) and DPEphos (20 mol %) were used. Phth = phthaloyl. TBS = *tert*-butylsilyl.

Table 3. Control Experiments



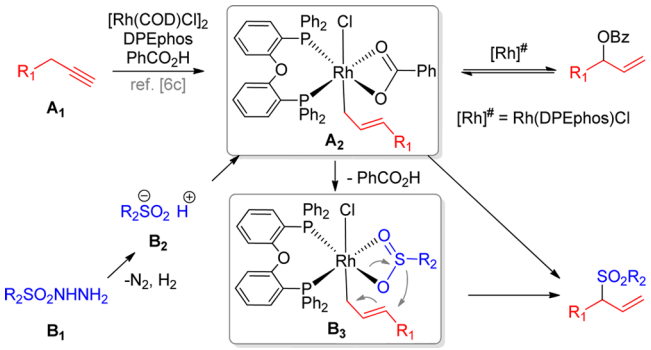
entry	E1–E3	*n* (equiv)	N1, N2	*z* (mol %)	yield/%[a]
1	**E1**	1.5	**N1**	0	59
2	**E1**	1.5	**N1**	50	61
3	**E2**	1.5	**N1**	0	25
4	**E2**	1.5	**N1**	50	70
5	**E1**	1.5	**N2**	0	80
6	**E1**	1.5	**N2**	50	77
7	**E2**	1.5	**N2**	0	trace[b]
8	**E2**	1.5	**N2**	50	trace[b]
9	**E3**	2.5	**N2**	0	n.r.[b]
10	**E3**	2.5	**N2**	50	n.r.[b]

[a]Isolated yield. [b]Determined by ^{1}HNMR of the crude reaction mixture; n.r.: no reaction.

According to the control experiments and a previous mechanistic investigation on rhodium-catalyzed coupling of carboxylic acids with terminal alkynes,[6c] we propose that the reaction of sulfonyl hydrazides with terminal alkynes proceeds via the following pathways (Scheme 2):[14] (1) A terminal alkyne

dx.doi.org/10.1021/ja509383r | J. Am. Chem. Soc. 2014, 136, 16124–16127

Scheme 2. Proposed Reaction Pathways

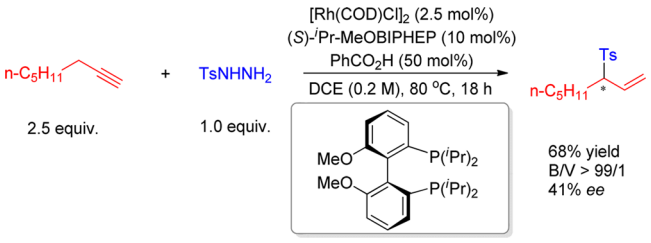


(**A1**) is transferred to a σ or π rhodium-allyl species (**A2**) via an alkyne-to-allene isomerization followed by hydrometalation in the presence of rhodium/DPEphos/benzoic acid. (2) The rhodium-allyl species (**A2**) can be attacked by an *in situ* formed sulfonyl anion to generate the desired branched allylic sulfone. Alternatively, ligand exchange of **A2** to **B3** followed by reductive elimination is also possible. The rhodium-allyl species (**A2**) undergoes reductive elimination to produce the branched allylic benzoate and [Rh(DPEphos)Cl], which is reversible. As a side reaction, the vinyl sulfones are formed via reductive elimination of the rhodium-vinyl species, which are generated by hydrometalation of rhodium hydride species to the terminal alkyne.

We speculate that a relatively weak acidity (pK_a around 4.0) of the reaction mixture is crucial. The *in situ* formed sulfinic acid is consumed promptly via reaction with **A2**; therefore, the overall acidity of the reaction is dominated by the acidity of benzoic acid.

To explore the potential of this methodology in asymmetric synthesis, a preliminary chiral ligand screening was undertaken. One result with the chiral ligand (*S*)-^{i}Pr-MeOBIPHEP, the branched allylic sulfone (**1a**), was obtained with a 68% isolated yield, excellent regioselectivity (B/V > 99/1), and a promising 41% *ee* (Scheme 3).

Scheme 3. Asymmetric Hydrosulfination



Synthesis of **1a** in a 5.0 mmol scale under the scope conditions led to the isolation of 1.14 g (86%) of the desired product without detrimental effect of the regioselectivity, which proved the practicality of this methodology.[13]

To conclude, we have developed the first rhodium/benzoic acid catalyzed hydrosulfination of terminal alkynes with sulfonyl hydrazides to afford valuable branched allylic sulfones in good to excellent yields and selectivities. The success of the hydrosulfination is a proof-of-concept of transforming terminal alkynes to branched allylic derivatives via rhodium/benzoic acid catalysis. Application of this methodology to other nucleophiles, their asymmetric variants, as well as mechanistic investigations will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytic data for synthesized compounds, including ^{1}H and ^{13}C NMR spectra as well as HPLC data sheets for chiral compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

bernhard.breit@chemie.uni-freiburg.de

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the DFG, the International Research Training Group "Catalysts and Catalytic Reactions for Organic Synthesis" (IRTG 1038), the Fonds der Chemischen Industrie, and the Krupp Foundation. We thank Umicore, BASF, and Wacker for generous gifts of chemicals.

■ REFERENCES

(1) Reviews on transition-metal-catalyzed allylic substitution: (a) Trost, B. M. *Chem. Rev.* **1996**, *96*, 395−422. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2943. (c) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258−297.

(2) Transition-metal-catalyzed allylic C−H functionalization: (a) Liu, G.; Wu, Y. *Top. Curr. Chem.* **2010**, *292*, 195−209. (b) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346−1347. (c) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328−6335. (d) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978−11987.

(3) Coupling of pronucleophiles with allenes: (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019−6020. (b) Al-Masum, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3809−3810. (c) Zimmer, R.; Dinesh, C.; Nandanan, E.; Khan, A. F. *Chem. Rev.* **2000**, *100*, 3067−3125. (d) Johnson, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923−2924. (e) Trost, B. M.; Jakel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438−4439. (f) Nishina, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314−3317. (g) Lalonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2352−2453. (h) Kim, I. S.; Krische, M. J. *Org. Lett.* **2008**, *10*, 513−515. (i) Kawamoto, T.; Hirabayashi, S.; Guo, X.; Nishimura, T.; Hayashi, T. *Chem. Commun.* **2009**, 3528−3530. (j) Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6916−6917. (k) Moran, J.; Preetz, A.; Mesch, R. A.; Krische, M. J. *Nat. Chem.* **2011**, *3*, 287−290. (l) Butler, K. L.; Tragni, M.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5175−5178.

(4) (a) Koschker, P.; Lumbroso, A.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 20746−20749. (b) Cooke, M. L.; Xu, K.; Breit, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 10876−10879. (c) Li, C.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 862−865. (d) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 2162−2165. (d) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 7268−7271.

(5) Examples on the coupling of pronucleophiles with alkynes for the synthesis of allylic products: (a) Trost, B. M.; Brieden, W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1335−1336. (b) Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622−1623.

(6) (a) Lumbroso, A.; Koschker, P.; Vautravers, N. R.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 2386−2389. (b) Lumbroso, A.; Abermil, N.; Breit, B. *Chem. Sci.* **2012**, *3*, 789−793. (c) Gellrich, U.; Meißner, A.; Steffani, A.; Kähny, M.; Drexler, H.; Heller, D.; Plattner, D. A.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 1097−1104.

(7) (a) Ballini, R.; Marcantoni, E.; Petrini, M. *Tetrahedron* **1989**, *45*, 6791−6798. (b) Wang, T.; Wang, F.; Yang, F.; Tian, S. *Chem.*

Commun. **2014**, *50*, 3802−3805. (c) Taniguchi, T.; Idota, A.; Ishibashi, H. *Org. Biomol. Chem.* **2011**, *9*, 3151−3153. (d) Yang, F.; Ma, X.; Tian, S. *Chem.—Eur. J.* **2012**, *18*, 1582−1585. (e) Wei, W.; Liu, C.; Yang, D.; Wen, J.; You, J.; Suo, Y.; Wang, H. *Chem. Commun.* **2013**, *49*, 10239−10241.

(8) (a) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581−5582. (b) Wucher, B.; Moser, M.; Schumacher, S. A.; Rominger, F.; Kunz, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 4417−4421.

(9) Sulfonyl hydrazides can be obtained in one step by reaction of commercially available sulfonyl chlorides with hydrazine.

(10) (a) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon: Oxford, 1993. (b) Patai, S.; Rapoport, Z.; Stirling, C. *The Chemistry Functional Groups: Sulfones and Sulfoxides*; Wiley: New York, 1988. (c) *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2008. (d) El-Awa, A.; NoShi, M. N.; Mollat du Jourdin, X.; Fuchs, P. L. *Chem. Rev.* **2009**, *109*, 2315−2349. (e) Alba, A. R.; Companyó, X.; Rios, R. *Chem. Soc. Rev.* **2010**, *39*, 2018−2033.

(11) (a) Chen, X.; Hussain, S.; Parveen, S.; Xhang, S.; Yang, Y.; Zhu, C. *Curr. Med. Chem.* **2012**, *19*, 3578−3604. (b) Morgan, A. S.; Sanderson, P. E.; Borch, R. F.; Tew, K. D.; Niitsu, Y.; Takayama, T.; Von Hoff, D. D.; Izbicka, E.; Mangold, G.; Paul, C.; Broberg, U.; Mannervik, B.; Henner, W. D.; Kauvar, L. M. *Cancer Res.* **1998**, *58*, 2568−2575. (c) Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. *J. Med. Chem.* **2005**, *48*, 499−506. (d) Bohl, E. C.; Gao, W.; Miller, D. D.; Bell, C. E.; Dalton, J. T. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 6201−6206. (e) Percicot, C. L.; Schnell, C. R.; Debon, C.; Hariton, C. *J. Pharmacol. Toxicol. Methods* **1996**, *36*, 223−228. (f) Buynak, J. D.; Doppalapudi, V. R.; Rao, A. S.; Nidamarthy, S. D.; Adam, G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 847−851. (g) Pilkiewicz, F. G.; Boni, L.; Mackinson, C.; Portnoff, J. B.; Scotto, A. An inhalation system for prevention and treatment of intracellular infections. WO 2003075889 A1, Sep 18, 2003.

(12) (a) Jegelka, M.; Plietker, B. *Org. Lett.* **2009**, *11*, 3462−3465. (b) Ueda, M.; Hartwig, J. F. *Org. Lett.* **2010**, *12*, 92−94. (c) Jegelka, M.; Plietker, B. *Chem.—Eur. J.* **2011**, *17*, 10417−10430. (d) Wu, X.; Chen, Y.; Li, M.; Zhou, M.; Tian, S. *J. Am. Chem. Soc.* **2012**, *134*, 14694−14697.

(13) See Supporting Information.

(14) Control experiments of 4-methyl-*N*′-(oct-1-en-3-yl)benzenesulfonohydrazide under optimized conditions (both without and with 50% benzoic acid) only led to decomposition, which indicates that nitrogen attack of the sulfonyl hydrazide to the *in situ* formed rhodium-allyl benzoate species **A2** followed by the release of nitrogen and hydrogen is unlikely.