Communication

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

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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

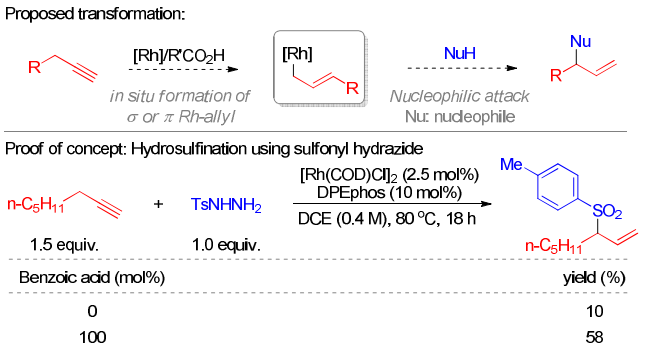
Supporting Information Placeholder

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 the last 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] towards 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 aicds with terminal alkynes indicated that the reaction involves rhodium/carboxylic acid catalyzed isomerization of 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 *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 a α–chiral center are an important class of compounds in biological research. For example, Dorzolamide, Tazobactam and Dalfopristin are prescription drugs used for anti-glaucoma agent, antibiotic treatments and anti-infections respectively.[11e-g] Herein, we report a rhodium catalyzed hydrosulfination of terminal alkynes with sulfonyl hydrazides as an efficient method to the synthesis of branched allylic sulfones.[7b,12]

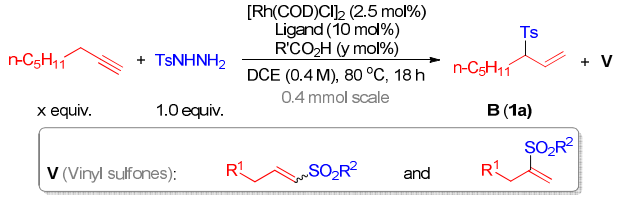
Scheme 1. Transformation of Terminal Alkynes to Branched Allylic Sulfones



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 hours with 1.0 equivalent benzoic acid. To our delight, the reaction gave a promising 58% nmr yield of the branched allylic sulfone (B), albeit 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 selectivi-

ty (Table 1, entry 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, entry 6-7). The branched allylic product (**1a**) was isolated with 92% yield when higher alkyne loading (2.5 equiv.) was used (Table 1, entry 8). Other carboxylic acids with different pKa value were proved to be less efficient than benzoic acid (Table 1, entry 9-10). Control experiments indicated that both the rhodium precursor and the ligand were necessary for the reaction to proceed.[13]

Table 1. Optimization of Rh-Catalyzed Hydrosulfination

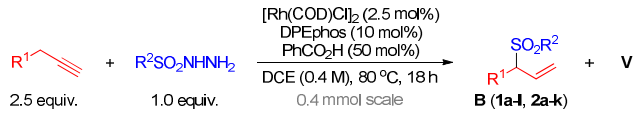


Entry	Ligand	x	R'	y	Yield/% [a]	B/V [b]
1	DPEphos	1.5	Ph	100	58	92/8
2	dppb	1.5	Ph	100	12	93/7
3	dppp	1.5	Ph	100	23	97/3
4	dppf	1.5	Ph	100	47	92/8
5	*rac*-binap	1.5	Ph	100	35	63/37
6	DPEphos	1.5	Ph	20	47	80/20
7	DPEphos	1.5	Ph	50	64	91/9
8	DPEphos	2.5	Ph	50	(92)[c]	93/7
9	DPEphos	2.5	CH_3	50	35	58/42
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 = l,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**), 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**).

Table 2. Scope of Rh-Catalyzed Hydrosulfination



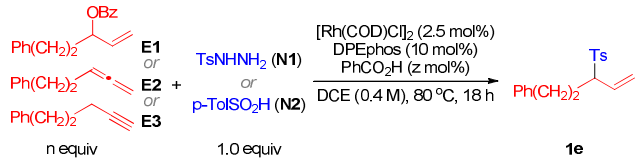
Entry	R^1	R^2	Yield/% [a]	B/V [b]
1	n-C_5H_{11}	p-Tol	92 (**1a**)	93/7
2	n-C_4H_9	p-Tol	82 (**1b**)	94/6
3	$(CH_3)_2CH$	p-Tol	63 (**1c**)[c]	79/21
4	Cyclopentyl	p-Tol	61 (**1d**)[c]	82/18
5	$Ph(CH_2)_2$	p-Tol	90 (**1e**)	93/7
6	$PhCH_2$	p-Tol	83 (**1f**)	93/7
7	Ph	p-Tol	70 (**1g**)[c]	82/18
8	$NC(CH_2)_2$	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.

To probe the reaction mechanism, control experiments of $TsNHNH_2$ (**N1**) and 4-methylbenzenesulfinic acid (**N2**) with branched benzoic ester (**E1**), allene (**E2**) and alkyne (**E3**) were performed (Table 3). Benzoic acid had little impact on the reactivity of ester (**E1**) with $TsNHNH_2$ (Table 3, Entry 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 allene (**E2**) with $TsNHNH_2$ was accelerated in the presence of 50% benzoic acid (Table 3, Entry 3-4), which indicates that benzoic acid is essential for the formation of rhodium-allyl species.

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

Table 3. Control experiments



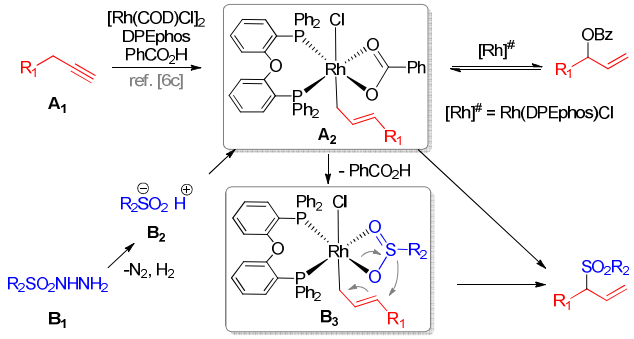
Entry	E1 - E3	n (equiv)	N1, N2	z (mol%)	Yield/%[a]
1	**E1**	1.5	**N1**	0	59
2	**E1**	1.5	**N1**	50	61
3	**E2**	1.5	**N1**	0	25
4	**E2**	1.5	**N1**	50	70
5	**E1**	1.5	**N2**	0	80
6	**E1**	1.5	**N2**	50	77
7	**E2**	1.5	**N2**	0	trace[b]
8	**E2**	1.5	**N2**	50	trace[b]
9	**E3**	2.5	**N2**	0	n.r[b]
10	**E3**	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 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) Terminal alkyne (**A1**) is transferred to a σ or π rhodium-allyl species (**A2**) via alkyne to allene isomerization followed by hydrometallation in the presence of rhodium/DPEphos/benzoic acid; 2) The rhodium-allyl species (**A2**) can be attacked by *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 hydrometallation of rhodium hydride species to terminal alkyne.

We speculate that a relatively weak acidity (pka 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.

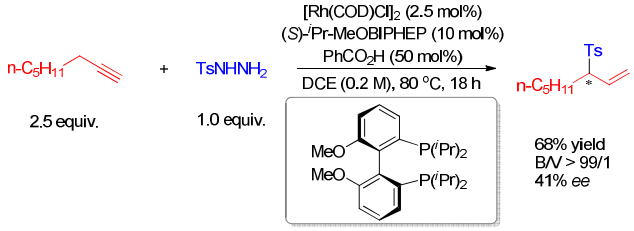
Scheme 2. Proposed reaction pathways



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 68% isolated yield, excellent regioselectivity (B/V > 99/1) and a promising 41% *ee* (Scheme 3).

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]

Scheme 3. Asymmetric hydrosulfination



To conclude, we have developed the first rhodium/benzoic acid catalyzed hydrosulfination of terminal alkynes with sulfonyl hydrazides to afford the valuable branched allylic sulfones in good to excellent yields and selectivities. The success of 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

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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. *Nature 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 obtianed in one step by reaction of commercially available sulfonyl chlorides with hydrazine.

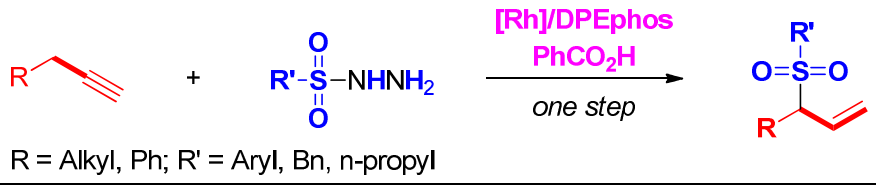
(10) (a) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon: Oxford, 1993; (b) Patai, S.; Rapoport, Z.; Stirling, C. *The Chemistry Functional Groups: Sulfones and Sulfoxides*; Wiley: New york, 1988; c) *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, 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*. **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. Che. Soc.* **2012**, *134*, 14694-14697.

(13) See supporting information.

(14) Control experiments of 4-methyl-*N*'-(oct-1-en-3-yl)benzenesulfonohydrazide under optimized condition (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 releasing of nitrogen and hydrogen is unlikely.



R = Alkyl, Ph; R' = Aryl, Bn, n-propyl