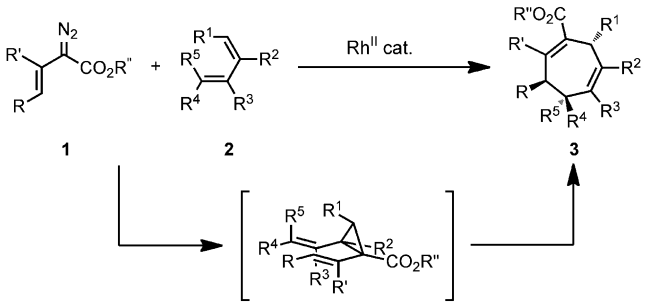
Asymmetric Catalysis

DOI: 10.1002/ange.201304310

Rhodium-Catalyzed Tandem Cyclopropanation/Cope Rearrangement of 4-Alkenyl-1-sulfonyl-1,2,3-triazoles with Dienes**

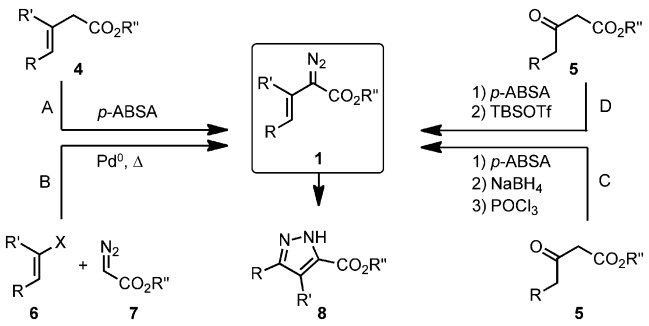
*Brendan T. Parr and Huw M. L. Davies**

Metal-catalyzed decomposition of diazo compounds to form transient donor/acceptor rhodium carbenes has been a general strategy for modern metallocarbene chemistry.[1] The stabilization afforded by a π-donating substituent on the carbenes enhances their selectivity, leading to a number of synthetically useful intermolecular transformations, such as enantioselective cyclopropanation[2] and C–H insertion.[3] Alkenyl substituents not only stabilize the carbene, but also participate in a number of novel tranformations.[4] One of the most versatile examples is the formal [4+3] cycloaddition reaction[5,6] (Scheme 1), which occurs via a tandem cyclopropanation/Cope rearrangement. As such, the reaction has found broad application in the total syntheses of complex natural products.[6]



Scheme 1. Rhodium(II)-catalyzed formal [4+3] cycloaddition.

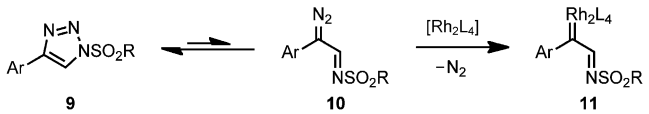
The standard approach for generating the alkenylcarbene precursor involves treatment of the corresponding β,γ-unsaturated ester **4** with a diazo transfer reagent, typically *p*-acetamidobenzenesulfonyl azide (*p*-ABSA), in the presence of an amine base, as shown in Scheme 2 (method A).[7] Although this approach to diazotization is robust for the synthesis of styryldiazoacetates (**4**, R = Ar), it is less reliable when applied to non-conjugated alkenyldiazoacetates. Alternative approaches have been developed, such as palladium-catalyzed cross-coupling of diazoacetates **7** with olefinic (pseudo)halides **6** (method B) and reduction/dehydration of α-diazo-β-ketoesters (**5**, method C). A particularly useful approach involves exposure of 1,3-dicarbonyls **5** to diazo-transfer conditions, followed by formation of the silylenolether (method D).[2b,8]



Scheme 2. Alkenyldiazoacetate syntheses and pyrazolization. *p*-ABSA = *p*-acetamidobenzenesulfonyl azide, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

A general challenge associated with alkenyldiazoacetates **1**, however, is their propensity to undergo a 6π e⁻ electrocyclization with concomitant aromatization to pyrazoles **8**.[9] Formation of **8** is irreversible, and moreover, the pyrazole is prone to coordinating with the Rh^{II} complex, impeding catalysis. The rate of pyrazole formation is dependent upon the substituents on the alkenyl group. The unsubstituted and alkyl-substituted vinyldiazoacetates cyclize within hours at ambient temperature and, even when stored at −20 °C, require purification prior to use. Thus, although significant latitude is afforded to the diene partner in the formal [4+3] cycloaddition, the product architecture is limited by the accessibility and stability of fuctionalized alkenyldiazoacetates.

More recently, 1,2,3-triazoles (Scheme 3, **9**) have been shown to act as masked diazo compounds, which are capable of undergoing a "ring-to-chain isomerization" to expose diazo moiety **10**.[11,12a] In the presence of a dirhodium tetracarboxylate catalyst, the α-diazo imine can be decomposed to generate the metal-bound donor/acceptor carbene intermediate **11**. A number of groups have demonstrated the applica-



Scheme 3. 1-Sulfonyl-1,2,3-triazoles as carbene precursors.

[*] B. T. Parr, Prof. H. M. L. Davies
Department of Chemistry, Emory University
1515 Dickey Drive, Atlanta, GA 30322 (USA)
E-mail: hmdavie@emory.edu
Homepage: http://www.chemistry.emory.edu/faculty/davies/Home.html

[**] This work was supported by the National Science Foundation (CHE 1213246). We thank Dr. John Bacsa and Dr. Kelly Kluge (Emory University) for X-ray crystallographic analysis.

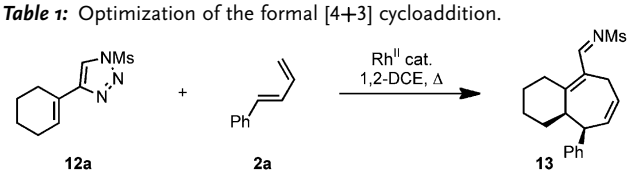
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201304310.

tion of *N*-sulfonyltriazoles as viable precursors in both classic (cyclopropanation and C–H insertion)[11] and novel rhodium carbene reactions.[13]

We have been interested in using 1,2,3-triazoles to expand the scope of donor groups that can be incorporated into donor/acceptor carbenes. To this end, we reported that 4-amido-1-sulfonyl-1,2,3-triazoles can be used to introduce a *N*-phthalimido donor group, which enabled an expedited synthesis of cyclopropyl amino acids.[13] Analogously, our group discovered that 4-alkenyl-1,2,3-triazoles exhibit a proclivity to undergo intramolecular electrocyclization, to generate a pyrrole product.[14] Herein, we describe that 4-alkenyl-1,2,3-triazoles are versatile diazo surrogates that can be used to broaden the range of rhodium-stabilized alkenylcarbenes for the formal [4+3] cycloaddition.

Our exploratory studies commenced with the 4-cyclohexenyl-triazole **12a**, which was previously prepared from the commercially available enyne and demonstrated to be suitable for the rhodium-catalyzed cyclopropanation of styrene.[11a] Using 1-phenyl-1,3-butadiene (**2a**) as the test substrate and standard conditions for cyclopropanation of alkenes with 1-sulfonyl-1,2,3-triazoles,[11a] an array of chiral dirhodium tetracarboxylate catalysts were examined (Table 1,

Table 1: Optimization of the formal [4+3] cycloaddition.



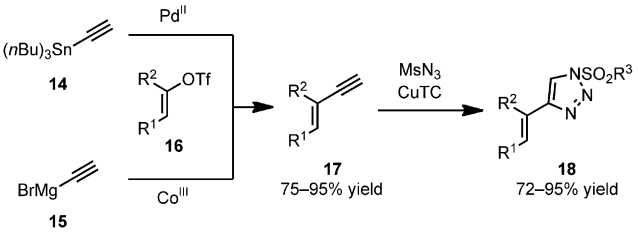
12a **2a** **13**

Entry	Rh^{II} cat.	*T* [°C]	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	$[Rh_2\{(S)\text{-dosp}\}_4]$	70	70	>30:1	−16
2	$[Rh_2\{(S)\text{-btpcp}\}_4]$	70	56	>30:1	15
3	$[Rh_2\{(S)\text{-pta}\}_4]$	70	80	>30:1	40
4	$[Rh_2\{(S)\text{-ptad}\}_4]$	70	67	>30:1	66
5	$[Rh_2\{(S)\text{-pttl}\}_4]$	70	48	>30:1	82
6	$[Rh_2\{(S)\text{-nttl}\}_4]$	70	75	>30:1	92
7	$[Rh_2\{(S)\text{-nttl}\}_4]$	60	82	>30:1	97
8	$[Rh_2\{(S)\text{-nttl}\}_4]$	50	69	>30:1	97

[a] Yield of isolated **13**. [b] Diastereoselectivity determined by ^{1}H NMR analysis of the crude residue. [c] Enantioselectivity determined by HPLC analysis on a chiral stationary phase. (*S*)-btpcp = (*S*)-1-(4-bromophenyl)-2,2-diphenylcyclopropanecarboxylate, DCE = dichloroethane, (*S*)-dosp = 4-(dodecylphenyl)sulfonyl-(2*S*)-prolinate], Ms = methanesulfonyl, (*S*)-nttl = *N*-naphthoyl-(*S*)-*tert*-leucinate, (*S*)-pta = *N*-phthaloyl-(*S*)-alanine, (*S*)-ptad = *N*-phthaloyl-(*S*)-adamantylglycine.

entries 1–6). To this end, $[Rh_2\{(S)\text{-nttl}\}_4]$ (entry 6) was the most efficacious for inducing both high yields and high levels of enantioselectivity for formation of **13** (75% yield, >30:1 d.r., 92% *ee*).[15] A decrease in temperature from 70 to 60°C (entries 6 and 7, respectively) brought about an improvement in both yield and enantioselectivity (82% yield, >30:1 d.r., 97% *ee*), but further reduction of reaction temperature was detrimental in terms of overall yield (entry 8).

Having established that a 4-alkenyl-1,2,3-triazole could be effectively used in the formal [4+3] cycloaddition, practical syntheses to generate a variety of triazoles **18** were developed,

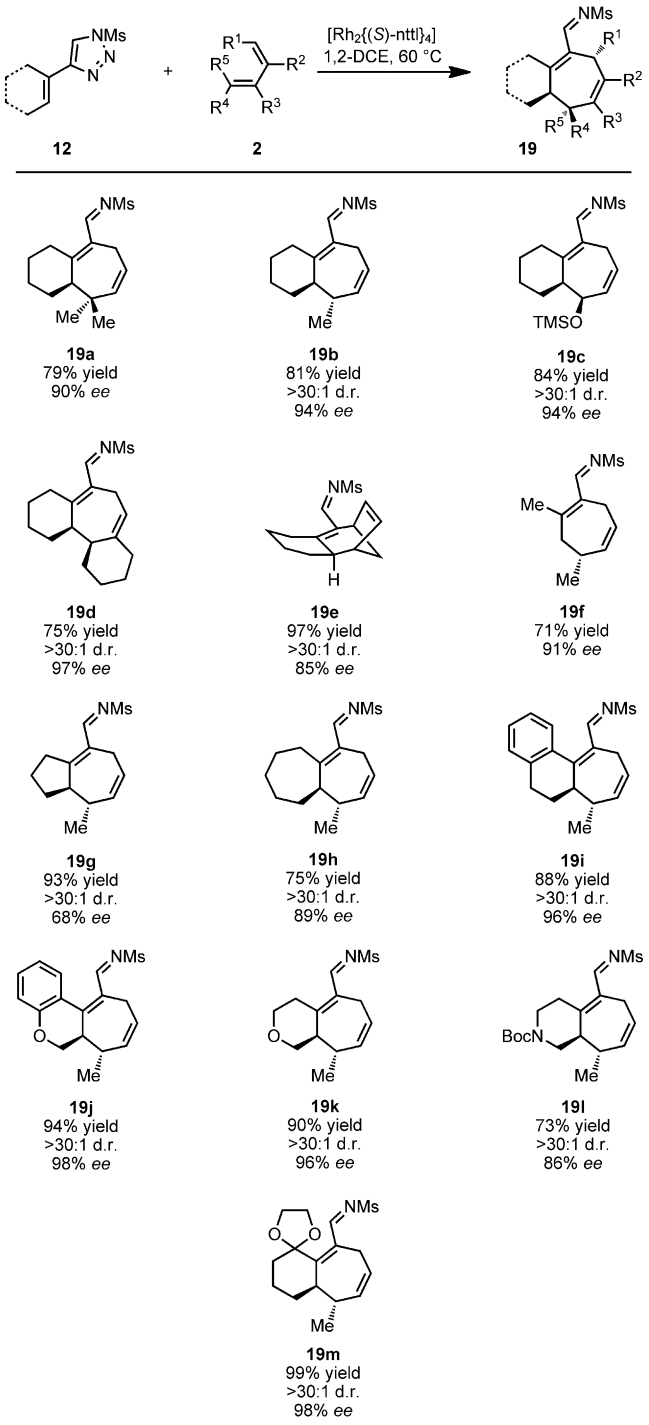


Scheme 4. Synthesis of 4-alkenyl-1-sulfonyl-1,2,3-triazoles. CuTC = copper thiophene carboxylate.

as illustrated in Scheme 4. Enynes **17** were prepared in a single step through a number of well-established cross-coupling reactions with an organometallic acetylide. Specifically, we found that both the Stille coupling of stannane **14**[16] and the Kumada coupling of Grignard reagent **15**[17] were both general and high yielding (75–95% yield) procedures for the synthesis of **17**. The subsequent copper-catalyzed azide/alkyne cycloaddition of **17** with mesyl azide provided access to the 4-alkenyl-1,2,3-triazole **18**, and was compatible with a range of functional groups (Scheme 4).[18] As the triazole is thermodynamically favored over the diazo imine isomer (Scheme 3), the undesirable rearrangement of the triazole to a pyrazole was not observed.

Following the optimization studies of the [4+3] cycloaddition, we were interested in determining whether the reaction would prove general for both the alkenylcarbene and diene partners. The results of these studies are reported in Scheme 5. Reaction of **12a** with 4,4′-disubstituted (**2b**), (*Z*)-4-substituted (**2c**) and (*E*)-4-substituted (**2d**) 1,3-dienes provided the corresponding cycloheptadienes (**19a–c**) in uniformly high yield and enantioselectivity (79–84% yield, 90–94% *ee*). When vinylcyclohexene (**2e**) was used, the semi-symmetric tricyclic [4.4.3.0] product **19d** was isolated in good yield and excellent stereoselectivity (75% yield, >30:1 d.r., 97% *ee*). Moreover, bridged tricyclic products could be prepared from reaction with cyclopentadiene (**2f**). Indeed, the cyclic diene provided the cycloadduct (**19e**) in very high yield and good enantioselectivity (98% yield, 85% *ee*).

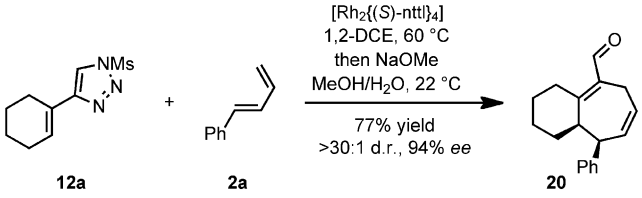
Proceeding with *cis*-1,3-pentadiene (**2c**) as the nucleophile, we then investigated the scope of the alkenylcarbene precursor (**12b–i**). Another triazole readily available from a commercial enyne, **12b** was first tested in the cycloaddition chemistry. The cycloheptadiene **19f** was formed in good yield and enantioselectivity (Scheme 5). We were more interested, however, in implementing this chemistry as a means to generate a variety of bicyclic [5.*n*.0] products. Thus, we moved forward with the study of varying ring sizes and substitution patterns for various 4-alkenyl-1,2,3-triazoles. A decrease in enantioselectivity was observed when the cyclopentenyl-substituted triazole **12c** was the carbene precursor (**19g**, 93% yield, 68% *ee*). Interestingly, the cycloheptenyl derivative **12d**, performed comparably to **12a**, affording the bicyclo[5.5.0]dodecane (**19h**) skeleton in 75% yield and 89% *ee*. Triazoles bearing an α-fused arene substituent (**12e** and **12f**) were particularly effective substrates, generating the corresponding angular tricyclic products (**19i** and **19j**) in excellent yield and stereoselectivity. The absolute configura-



Scheme 5. Scope of the formal [4+3] cycloaddition. Yields shown are of isolated products. Diastereoselectivity determined by ^{1}H NMR analysis of the crude residue. Enantioselectivity determined by HPLC analysis on a chiral stationary phase. Boc = *tert*-butoxycarbonyl.

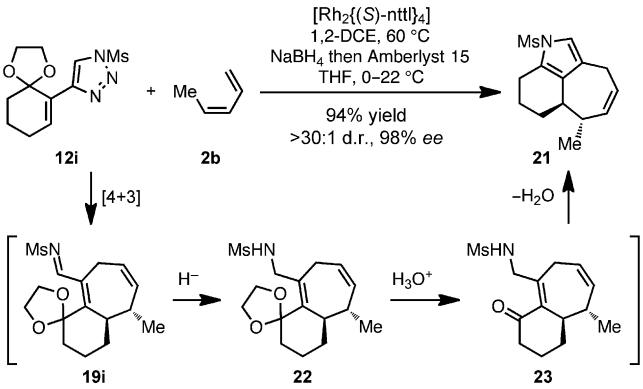
tion of the latter compound was established by single-crystal X-ray crystallographic analysis and the stereochemistry of the series of products was assigned by analogy.[19] Heterocyclic alkenyl donor-groups were also well tolerated, as demonstrated in the syntheses of **19k** and **19l**. Thus, the fused pyranyl and piperidinyl ring systems were generated in high enantioselectivity (96% and 86% *ee*, respectively). The more hindered diazo precursor **12i**, which bears an α-quaternary carbon, was in fact the most efficient substrate overall. The ketal-bearing product **19m** was isolated in 99% yield and 98% *ee*.

As the products of the formal [4+3] cycloaddition contain a synthetically useful α,β-unsaturated imine moiety, we sought to demonstrate sequential one-pot manipulations could be conducted without epimerization of the γ-chiral center. Indeed, formal [4+3] cycloaddition of **12a** and **2a** followed by basic hydrolysis afforded the α,β-unsaturated aldehyde **20** in high yield with no observable epimerization (Scheme 6). The absolute configuration of **20** was further verified by X-ray crystallographic analysis.[19]



Scheme 6. One-pot synthesis of α,β-unsaturated aldehyde **20**.

The combined utility of an appropriately chosen donor group and the readily functionalized imine group are exemplified in Scheme 7. Following the cycloaddition reaction with triazole **12i**, reduction of the imine was achieved



Scheme 7. One-pot synthesis of tetrahydroindole **21**.

with sodium borohydride to provide **22**. Subsequent acid-catalyzed opening of the ketal was induced by Amberlyst 15 resin, with the effect of concomitant cyclodehydration, through the intermediacy of **23**, to generate the tetrahydroindole **21** in 94% yield for the one-pot process.

In conclusion, we have developed a practical method for the synthesis of structurally diverse rhodium alkenylcarbenes from bench-top-stable 1-sulfonyl-1,2,3-triazole precursors. The reaction is general for a broad range of 4-alkenyl-1,2,3-triazoles and dienes, enabling the stereoselective synthesis of a variety of polycyclic imines, which are readily converted into amines or aldehydes in a one-pot process. The new entry into alkenylcarbenes enables the engineering of complex sub-

strates capable of subsequent transformations, which will likely be of value for expedited syntheses of natural products.

Experimental Section

Representative procedure for the synthesis of **13**: A 1,2-dichloroethane (1.5 mL) solution of 1,3-phenylbutadiene (**2a**) (130 mg, 1.0 mmol) was added to an Ar-purged culture tube containing **12a** (114 mg, 0.50 mmol) and $[Rh_2\{(S)\text{-nttl}\}_4]$ (7 mg, 0.005 mmol). The reaction vessel was immersed in an oil bath heated to 60 °C and stirred for 6 h. The product was then purified directly by flash chromatography (SiO_2, hexanes/EtOAc 80:20) to give a white solid (132 mg, 82 % yield).

Received: May 19, 2013
Published online: August 1, 2013

Keywords: carbenes · cope rearrangement · cycloaddition · cyclopropanation · rhodium

[1] a) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**; b) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861 – 2904; c) H. M. L. Davies, J. R. Denton, *Chem. Soc. Rev.* **2009**, *38*, 3061 – 3071; d) H. M. L. Davies, S. A. Panaro, *Tetrahedron* **2000**, *56*, 4871 – 4880; e) J. Hansen, J. Autschbach, H. M. L. Davies, *J. Org. Chem.* **2009**, *74*, 6555 – 6563; f) H. M. L. Davies, A. M. Walji in *Modern Rhodium-Catalyzed Organic Reactions* (Ed.: P. A. Evans), Wiley-VCH, Weinheim, **2005**, pp. 301 – 340.

[2] a) H. M. L. Davies, R. J. Townsend, *J. Org. Chem.* **2001**, *66*, 6595 – 6603; b) P. Müller, G. Bernardinelli, Y. F. Allenbach, M. Ferri, H. D. Flack, *Org. Lett.* **2004**, *6*, 1725 – 1728.

[3] a) H. M. L. Davies, T. Hansen, M. R. Churchill, *J. Am. Chem. Soc.* **2000**, *122*, 3063 – 3070; b) H. M. L. Davies, P. Ren, *J. Am. Chem. Soc.* **2001**, *123*, 2070 – 2071; c) H. M. L. Davies, T. Hansen, D. W. Hopper, S. A. Panaro, *J. Am. Chem. Soc.* **1999**, *121*, 6509 – 6510.

[4] a) X. Wang, X. Xu, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* **2011**, *133*, 16402 – 16405; b) B. T. Parr, Z. Li, H. M. L. Davies, *Chem. Sci.* **2011**, *2*, 2378 – 2382; c) H. M. L. Davies, Y. Lian, *Acc. Chem. Res.* **2012**, *45*, 923 – 935; d) H. M. L. Davies, B. Xiang, N. Kong, D. G. Stafford, *J. Am. Chem. Soc.* **2001**, *123*, 7461 – 7462; e) M. P. Doyle, M. Yan, W. Hu, L. S. Gronenberg, *J. Am. Chem. Soc.* **2003**, *125*, 4692 – 4693; f) Y. Lian, H. M. L. Davies, *Org. Lett.* **2012**, *14*, 1934 – 1937.

[5] a) H. M. L. Davies, D. G. Stafford, B. D. Doan, J. H. Houser, *J. Am. Chem. Soc.* **1998**, *120*, 3326 – 3331; b) L. Deng, A. J. Giessert, O. O. Gerlitz, X. Dai, S. T. Diver, H. M. L. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 1342 – 1343; c) H. M. L. Davies, T. J. Clark, H. D. Smith, *J. Org. Chem.* **1991**, *56*, 3817 – 3824.

[6] a) H. M. L. Davies, B. D. Doan, *J. Org. Chem.* **1998**, *63*, 657 – 660; b) A. S. Kende, T. L. Smalley, Jr., H. Huang, *J. Am. Chem. Soc.* **1999**, *121*, 7431 – 7432; c) J. P. Olson, H. M. L. Davies, *Org. Lett.* **2008**, *10*, 573 – 576; d) B. D. Schwartz, J. R. Denton, Y. Lian, H. M. L. Davies, C. M. Williams, *J. Am. Chem. Soc.* **2009**, *131*, 8329 – 8332; e) Y. Lian, L. C. Miller, S. Born, R. Sarpong, H. M. L. Davies, *J. Am. Chem. Soc.* **2010**, *132*, 12422 – 12425; f) J. Xu, E. J. E. Caro-Diaz, E. A. Theodorakis, *Org. Lett.* **2010**, *12*, 3708 – 3711.

[7] H. M. L. Davies, J. Yang, J. R. Manning, *Tetrahedron: Asymmetry* **2006**, *17*, 665 – 673.

[8] H. M. L. Davies, J. H. Houser, C. Thornley, *J. Org. Chem.* **1995**, *60*, 7529 – 7534.

[9] M. T. Supurgibekov, V. M. Zakharova, J. Sieler, V. A. Nikolaev, *Tetrahedron Lett.* **2011**, *52*, 341 – 345.

[10] a) S. Chuprakov, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 4463 – 4466; b) S. Chuprakov, F. W. Hwang, V. Gevorgyan, *Angew. Chem.* **2007**, *119*, 4841 – 4843; *Angew. Chem. Int. Ed.* **2007**, *46*, 4757 – 4759.

[11] a) S. Chuprakov, S. W. Kwok, L. Zhang, L. Lercher, V. V. Fokin, *J. Am. Chem. Soc.* **2009**, *131*, 18034 – 18035; b) N. Grimster, L. Zhang, V. V. Fokin, *J. Am. Chem. Soc.* **2010**, *132*, 2510 – 2511; c) S. Chuprakov, J. A. Malik, M. Zibinsky, V. V. Fokin, *J. Am. Chem. Soc.* **2011**, *133*, 10352 – 10355; d) T. Miura, T. Tanaka, T. Biyajima, A. Yada, M. Murakami, *Angew. Chem.* **2013**, *125*, 3975 – 3978; *Angew. Chem. Int. Ed.* **2013**, *52*, 3883 – 3886.

[12] a) T. Miura, T. Biyajima, T. Fujii, M. Murakami, *J. Am. Chem. Soc.* **2012**, *134*, 194 – 196; b) T. Miura, Y. Funakoshi, M. Morimoto, T. Biyajima, M. Murakami, *J. Am. Chem. Soc.* **2012**, *134*, 17440 – 17443; c) N. Selander, V. V. Fokin, *J. Am. Chem. Soc.* **2012**, *134*, 2477 – 2480; d) N. Selander, B. T. Worrell, S. Chuprakov, S. Velaparthi, V. V. Fokin, *J. Am. Chem. Soc.* **2012**, *134*, 14670 – 14673; e) M. Zibinsky, V. V. Fokin, *Angew. Chem.* **2013**, *125*, 1547 – 1550; *Angew. Chem. Int. Ed.* **2013**, *52*, 1507 – 1510; f) B. T. Parr, S. A. Green, H. M. L. Davies, *J. Am. Chem. Soc.* **2013**, *135*, 4716 – 4718; g) E. E. Schultz, R. Sarpong, *J. Am. Chem. Soc.* **2013**, *135*, 4696 – 4699; h) S. Chuprakov, S. W. Kwok, V. V. Fokin, *J. Am. Chem. Soc.* **2013**, *135*, 4652 – 4655.

[13] J. S. Alford, H. M. L. Davies, *Org. Lett.* **2012**, *14*, 6020 – 6023.

[14] J. S. Alford, J. E. Spangler, H. M. L. Davies, unpublished results.

[15] For syntheses of the catalysts used in this study, see: a) H. M. L. Davies, P. R. Bruzinski, D. H. Lake, N. Kong, M. J. Fall, *J. Am. Chem. Soc.* **1996**, *118*, 6897 – 6907; b) C. Qin, V. Boyarskikh, J. H. Hansen, K. I. Hardcastle, D. G. Musaev, H. M. L. Davies, *J. Am. Chem. Soc.* **2011**, *133*, 19198 – 19204; c) S.-I. Hashimoto, N. Watanabe, S. Ikegami, *Tetrahedron Lett.* **1990**, *31*, 5173 – 5174; d) R. P. Reddy, G. H. Lee, H. M. L. Davies, *Org. Lett.* **2006**, *8*, 3437 – 3440; e) P. Müller, Y. Allenbach, E. Robert, *Tetrahedron: Asymmetry* **2003**, *14*, 779 – 785.

[16] S. M. King, N. A. Calandra, S. B. Herzon, *Angew. Chem. Int. Ed.* **2013**, *125*, 3730 – 3733; *Angew. Chem. Int. Ed.* **2013**, *52*, 3642 – 3645.

[17] E. Shirakawa, T. Sato, Y. Imazaki, T. Kimura, T. Hayashi, *Chem. Commun.* **2007**, 4513 – 4515.

[18] J. Raushel, V. V. Fokin, *Org. Lett.* **2010**, *12*, 4952 – 4955.

[19] CCDC 938813 (**19j**) and 938623 (**20**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

