Heterocycles

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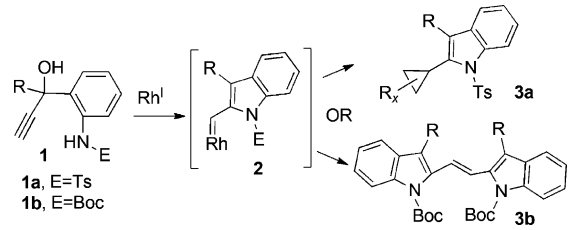
Divergent Reactivity of Rhodium(I) Carbenes Derived from Indole Annulations

Xiaoxun Li, Hui Li, Wangze Song, Po-Sen Tseng, Lingyan Liu, Ilia A. Guzei, and Weiping Tang**

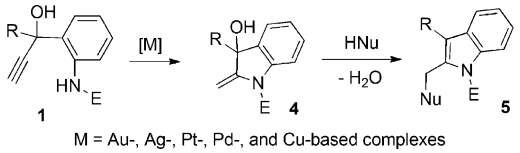
Abstract: *Rhodium(I) carbenes were generated from propargylic alcohol derivatives as the result of a dehydrative indole annulation. Depending on the choice of the electron-withdrawing group on the aniline nitrogen nucleophile, either a cyclopropanation product or dimerization product was obtained chemoselectively. Intramolecular hydroamidation occurred for the same type of propargylic alcohol derivatives when other transition-metal catalysts were employed.*

Metal carbenes are versatile intermediates for a variety of reactions.[1] They are generally derived from diazo compounds or related derivatives.[2] Fischer carbenes serve as the primary precursors of rhodium(I) carbenes,[3] with a few exceptions.[4] We[5] and others[6] discovered that rhodium(I) carbenes could be derived from 1,2-acyloxy migration of propargylic esters for cycloadditions.[7] Recently, we also found that 3-hydroxy-1,4-enynes could serve as rhodium(I) carbene precursors and as five-carbon components in [5+1] cycloaddition reactions.[8] In an effort to develop general carbene precursors for indole synthesis, we found that indole annulation of the propargylic alcohol **1** could produce the rhodium(I) carbene **2**, which either underwent chemoselective cyclopropanation or dimerization to form the products **3a** and **3b**, respectively, depending on the choice of the E group (Scheme 1). Although a related calcium-catalyzed tandem indole annulation and cyclopropanation involving multiple cationic species was developed by Niggemann and co-workers, only intramolecular cyclcopropanation was reported by tethering the alkene to the propargylic alcohol.[9]

Indole is one of the most abundant bioactive heterocycles in natural products and pharmaceutical agents.[10] Most previous indole syntheses focused on the construction of indole ring alone.[11] It would be more efficient to couple indole annulation with other transformations in a cascade manner. The propargylic alcohol **1** has been used by Chan and co-workers extensively for various gold- and silver-catalyzed tandem indole annulations and nucleophilic additions (Scheme 2).[12] We found that other catalysts, such as platinum-, palladium-, and copper-based complexes could also mediate this process.[13] Clearly, the rhodium(I) catalyst is unique in promoting the formation of the carbene **2**, instead of the hydroamidation product **4**, and subsequent divergent transformations.



Scheme 1. Divergent reactivity of rhodium(I)-carbenes derived from indole annulation. Boc = *tert*-butoxycarbonyl, Ts = 4-toluenesulfonyl.



Scheme 2. Metal-catalyst-mediated hydroamidation.

Diazomethanes without an adjacent electron-withdrawing group are generally not very stable and those with an electron-rich aryl substituent are particularly difficult to prepare.[14] Indeed, we were not able to prepare the indolyl-substituted diazomethane precursor for the carbene **2** using known methods,[14] and thus tried to explore alternative cyclopropanation methods.[15] A tandem indole annulation of **1** followed by cyclopropanation allows the construction of both indole and cyclopropane, two of the most important rings in organic chemistry.[10,16]

We began our investigation by examining various transition-metal catalysts which might mediate the cyclization of **6a** in the presence of the alkene **7a** (Table 1). Cationic rhodium(I) catalysts or neutral rhodium(I) catalysts without CO did not provide any desired product (entries 1–3). High yield of the product **8a** could be obtained by using the $[\{Rh(CO)_2Cl\}_2]$ complex as the catalyst in either the presence or absence of a CO balloon (entries 4 and 5). When the amount of alkene was reduced from 2 to 1.2 equivalents, a slightly lower yield was observed (entry 6). No cyclopropanation products were formed when other metal complexes were employed (entries 7–10). In some cases, the hydroamidation product **4** was observed, and was consistent with

[*] Dr. X. Li, H. Li, W. Song, P.-S. Tseng, Dr. L.-y. Liu, Prof. Dr. W. Tang
School of Pharmacy, University of Wisconsin-Madison
Madison, WI 53705-2222 (USA)
E-mail: wtang@pharmacy.wisc.edu
Dr. L.-y. Liu
Institute of Elemento-Organic Chemistry, College of Chemistry
Nankai University
Tianjin, 300071 (P.R. China)
E-mail: liulingyan@nankai.edu.cn
Dr. I. A. Guzei, Prof. Dr. W. Tang
Department of Chemistry, University of Wisconsin-Madison
Madison, WI 53706 (USA)

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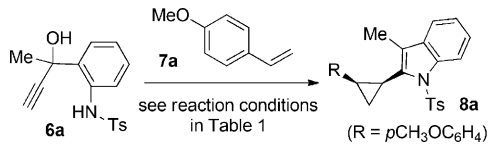
Table 1: Screening reaction conditions for cyclopropanation.[a]



Entry	Conditions	Yield [%][b]
1	$[Rh(cod)_2]BF_4$ (5 mol%)	0
2	$[Rh(PPh_3)_3Cl]$ (5 mol%)	0
3	$[\{Rh(cod)Cl\}_2]$ (5 mol%)	0
4	$[\{Rh(CO)_2Cl\}_2]$ (5 mol%), CO (1 atm)	82
5	$[\{Rh(CO)_2Cl\}_2]$ (5 mol%)	86
6	$[\{Rh(CO)_2Cl\}_2]$ (5 mol%)	77[c]
7	$[\{Ir(cod)Cl\}_2]$ (5 mol%)	0
8	$Pd(OAc)_2$ (5 mol%)	0
9	$PtCl_2$ (5 mol%)	0
10	$[Au(PPh_3)Cl]$ (5 mol%)	0

[a] Reaction conditions: dichloroethane (DCE), **6a** (1.0 equiv), **7a** (2.0 equiv), RT, 12–20 h, unless noted otherwise. [b] The yield was determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as the internal standard. [c] **7a** (1.2 equiv). cod = 1,5-cyclooctadiene.

previous reports.[12a–c,13] The tosyl group of **8a** can be removed as shown in the Supporting Information.

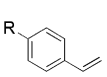
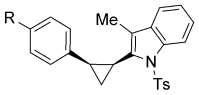
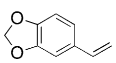
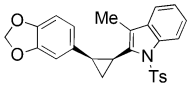
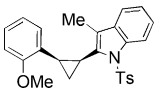
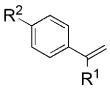
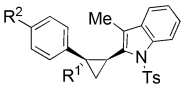
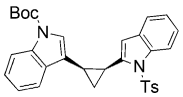
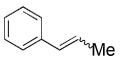
We then examined the scope with respect to the alkenes, using **6a** as the carbene precursor. Various styrenes with a *para* substituent participated in the cyclopropanation and yielded exclusively the *cis* diastereoisomer (Table 2, entries 1–4). The reactivity of electron-poor styrene was lower than that of electron-rich styrene (entry 1 versus entry 5). Styrenes with multiple substituents or an *ortho* substituent were also tolerated (entries 6 and 7). The structure of **8f**[22] was unambiguously determined by X-ray analysis. Trisubstituted cyclopropanes (**8h–j**) were successfully prepared from 1,1-disubstituted alkenes (entries 8–10). Notably, the free alcohols in **7i** and **7j** were tolerated under the standard reaction conditions. Heterocycles such as indole could also be introduced to the diaryl cyclopropane products (entry 11). Unfortunately, the 1,2-disubstituted alkene **7l** did not participate in the cyclopropanation. No cyclopropanation was observed by using alkenes with just an alkyl substituent, including both electron-rich vinyl ethers and electron-poor enones.

We next explored the scope with respect to the propargylic alcohols. The aryl sulfonyl group did not have an obvious effect to the tandem annulation/cyclopropanation (Table 3, entries 1–5). The R^1 group could be a hydrogen or other alkyl groups (entries 6–8). Substituents could be introduced to the benzene ring of the substrate **9i** (entry 9). Notably, the aryl bromide in **9i** could be tolerated for rhodium-catalyzed reactions.

The dienes **11a** and **11b** participated in the cyclopropanation and afforded the corresponding vinylcyclopropanes **12**, which could undergo Cope rearrangement to yield the cyclohepta[*b*]indole **14a** or **14b**, respectively (Scheme 3).[17] Cyclohepta[*b*]indole is present in a number of natural products[18] and bioactive pharmaceutical agents.[19]

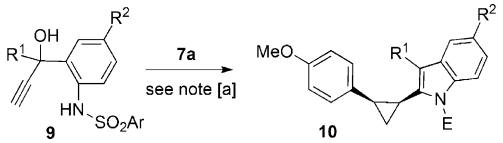
In addition to various arylsulfonyl groups shown in Table 3, we also explored the effect of other electron-with-

Table 2: Scope of alkenes for the tandem indole annulation/cyclopropanation with **6a**.[a]

Entry	Substrate **7**	Product **8** (d.r.)[b]	Yield [%][c]
			
1	**7a**, R = MeO	**8a** (20:1)	80
2	**7b**, R = H	**8b** (20:1)	48
3	**7c**, R = Me	**8c** (20:1)	68
4	**7d**, R = *t*Bu	**8d** (20:1)	70
5	**7e**, R = CF_3	**8e**	20[b]
			
6	**7f**	**8f** (20:1)	78
			
7	**7g**	**8g** (20:1)	70
			
8	**7h**, R^1 = Me, R^2 = H	**8h**, (20:1)	63
9	**7i**, R^1 = CH_2OH, R^2 = H	**8i**, (20:1)	52
10	**7j**, R^1 = CH_2OH, R^2 = MeO	**8j**, (20:1)	87
			
11[d]	**7k**	**8k** (20:1)	60
			
12	**7l** (*E*/*Z* = 1:1)	–	0

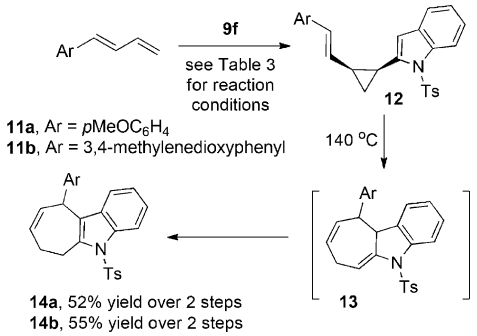
[a] Conditions: $[\{Rh(CO)_2Cl\}_2]$ (5 mol%), DCE, **6a** (1.0 equiv), **7** (2.0 equiv), RT, 12–20 h, unless noted otherwise. [b] Determined by ^{1}H NMR analysis of crude product. [c] Isolated yield. [d] Substrate **9f** (Table 3) was employed in this case.

Table 3: Scope of propargylic alcohols for the tandem indole annulation/cyclopropanation.[a]

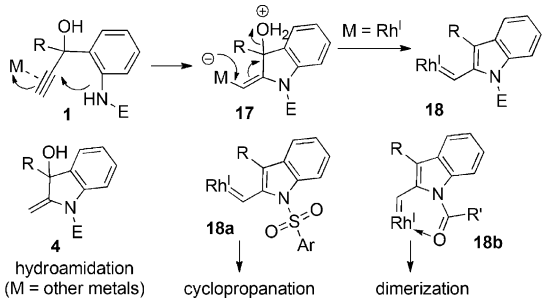


Entry	**9**	**10** (d.r.)[b]	Yield [%][c]
1	**9a**, R^1 = Me, R^2 = H, Ar = Ph	**10a** (20:1)	72
2	**9b**, R^1 = Me, R^2 = H, Ar = 4-FC_6H_4	**10b** (20:1)	77
3	**9c**, R^1 = Me, R^2 = H, Ar = 4-*t*BuC_6H_4	**10c** (20:1)	72
4	**9d**, R^1 = Me, R^2 = H, Ar = 4-MeOC_6H_4	**10d** (20:1)	73
5	**9e**, R^1 = Me, R^2 = H, Ar = 1-naphthyl	**10e** (20:1)	75
6	**9f**, R^1 = R^2 = H, Ar = 4-MeC_6H_4	**10f** (20:1)	66
7	**9g**, R^1 = Et, R^2 = H, Ar = 4-MeC_6H_4	**10g** (5:1)	81
8	**9h**, R^1 = *n*Bu, R^2 = H, Ar = 4-MeC_6H_4	**10h** (5:1)	77
9	**9i**, R^1 = Me, R^2 = Br, Ar = 4-MeC_6H_4	**10i** (20:1)	71

[a] Reaction conditions: $[\{Rh(CO)_2Cl\}_2]$ (5 mol%), DCE, **9** (1.0 equiv), **7a** (2.0 equiv), RT, 12–20 h, unless noted otherwise. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of isolated product.



Scheme 3. Sequential indole annulation, cyclopropanation, and Cope rearrangement.

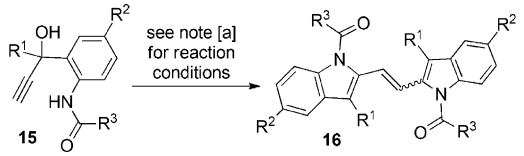


Scheme 4. Proposed mechanism for the formation of rhodium(I) carbenes and their divergent reactivity.

drawing groups on the aniline nucleophile for the tandem annulation/cyclopropanation. Under the standard reaction conditions outlined in Table 3, no cyclopropanation product was observed for the substrate **15a** (Table 4) in the presence of different styrenes. Instead, trace amounts of the dimeric indole **16a** were obtained in the presence or absence of styrenes. The yield of the dimeric indole was improved dramatically by simply attaching a CO balloon to the reaction flask (entry 1). Under these reaction conditions, we previously did not observe any dimeric indole for **6a**, having a tosyl group on the nitrogen atom (Table 1, entry 4). No dimerization products were formed when other metal complexes shown in entries 7–10 of Table 1 were employed.

Dimerization of carbenes is generally considered as a side reaction.[20] Given the high yield of **16a** and the potential utility of indole derivatives, we further examined the scope of

Table 4: Scope of indole dimerization.[a]



Entry	**15**		**16** (*E*/*Z*)[b]	Yield [%][c]
1	**15a**,	R^1 = Me, R^2 = H, R^3 = *t*BuO	**16a** (1.4:1)	81
2	**15b**,	R^1 = Me, R^2 = H, R^3 = MeO	**16b** (1.2:1)	81
3	**15c**,	R^1 = Me, R^2 = H, R^3 = CH_2=$CHCH_2CH_2$	**16c** (1.4:1)	82
4	**15d**,	R^1 = R^2 = H, R^3 = *t*BuO	**16d** (1.2:1)	88
5	**15e**,	R^1 = Et, R^2 = H, R^3 = *t*BuO	**16e** (1.3:1)	47;[d] 35[e]
6	**15f**,	R^1 = *i*Pr, R^2 = H, R^3 = *t*BuO	**16f** (1.3:1)	74
7	**15g**,	R^1 = *n*Bu, R^2 = H, R^3 = *t*BuO	**16g** (1.5:1)	46;[d] 34[e]
8	**15h**,	R^1 = Ph, R^2 = H, R^3 = *t*BuO	**16h** (1.1:1)	33;[d] 27[e]
9	**15i**,	R^1 = Me, R^2 = Br, R^3 = *t*BuO	**16i** (1.3:1)	92

[a] Reaction conditions: [{$Rh(CO)_2Cl$}$_2$] (5 mol%), CO (1 atm), DCE, **15a**, 60°C, 10 h, unless noted otherwise. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of the two isolated two isomers. [d] Yield of the isolated *E* isomer. [e] Yield of the isolated *Z* isomer.

the indole dimerization (Table 4). In addition to the Boc group, another alkoxy carbonyl group (entry 2) or acyl group (entry 3) also facilitated the formation of the dimer **16**. It is also interesting to note that the carbene intermediate cannot be trapped by an intramolecularly tethered alkene (entry 3). The R^1 substituent can be either a hydrogen, ethyl, isopropyl, butyl, or phenyl group (entries 4–8). Dimeric indoles with a bromine substituent on the benzene ring could also be prepared (entry 9). The *E* and *Z* isomers were easily separated by column chromatography in several cases. The structures of the dimeric indoles were unambiguously determined by X-ray analysis of (*E*)-**16b**[22] and (*Z*)-**16b**.[22]

The mechanism of the indole annulation/cyclopropanation or dimerization is proposed in Scheme 4. Coordination of the metal catalyst to alkyne in **1** will induce nucleophilic attack of the aniline nitrogen atom to form the adduct **17**.[12a–c] This process is promoted by an electron-withdrawing ligand, such as CO, on the rhodium(I) complexes.[7] Protonation to form the hydroamidation product **4** occurrs for most π-acidic transition metals.[12a–c] Elimination of water proceeds to yield the carbene intermediate **18**, which undergoes either cyclopropanation or dimerization, depending on the nature the E group. We propose that the chemoselectivity may arise from the ability of the carbonyl group in **18b** to better coordinate to rhodium(I) carbenes. The *cis*-selective cyclopropanation, based on the X-ray structure of **8f** and NMR data, is presumably because both aryl substituents prefer to be away from the metal complex, and is consistent with gold-catalyzed 1,2-acyloxy migration of propargylic esters/intermolecular cyclopropanation.[21]

In summary, various cyclopropanes with *cis*-1,2-diaryl substituents were prepared stereoselectively from propargylic alcohol derivatives by a tandem indole annulation and cyclopropanation. The enantioselective version of this cascade process is currently under investigation in our laboratory. Divergent reactivity was observed when the aniline nitrogen atom of the substrate is attached to different electron-withdrawing groups. Computational studies are ongoing to elucidate the origin of the intriguing chemoselectivity.

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Angew. Chem. **2015**, *127*, 13097–13100

[1] For selected reviews on reactions involving metal carbenes, see: a) M. P. Doyle, *Chem. Rev.* **1986**, *86*, 919; b) A. Padwa, S. F. Hornbuckle, *Chem. Rev.* **1991**, *91*, 263; c) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223; d) M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911; e) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861; f) H. M. L. Davies, S. J. Hedley, *Chem. Soc. Rev.* **2007**, *36*, 1109; g) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417; h) P. de Frémont, N. Marion, S. P. Nolan, *Coord. Chem. Rev.* **2009**, *253*, 862; i) H. M. L. Davies, J. R. Denton, *Chem. Soc. Rev.* **2009**, *38*, 3061; j) G. C. Vougioukalakis, R. H. Grubbs, *Chem. Rev.* **2010**, *110*, 1746.

[2] For selected reviews, see: a) T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091; b) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**; c) Z. Zhang, J. Wang, *Tetrahedron* **2008**, *64*, 6577.

[3] a) J. Barluenga, R. Vicente, L. A. Lopez, E. Rubio, M. Tomas, C. Alvarez-Rua, *J. Am. Chem. Soc.* **2004**, *126*, 470; b) J. Barluenga, R. Vicente, P. Barrio, L. A. Lopez, M. Tomas, *J. Am. Chem. Soc.* **2004**, *126*, 5974; c) J. Barluenga, R. Vicente, L. A. Lopez, M. Tomas, *J. Am. Chem. Soc.* **2006**, *128*, 7050; d) T. Nishimura, Y. Maeda, T. Hayashi, *Angew. Chem. Int. Ed.* **2010**, *49*, 7324; *Angew. Chem.* **2010**, *122*, 7482.

[4] a) H. Werner, *J. Organomet. Chem.* **1995**, *500*, 331; b) T. Nishimura, T. Kawamoto, M. Nagaosa, H. Kumamoto, T. Hayashi, *Angew. Chem. Int. Ed.* **2010**, *49*, 1638; *Angew. Chem.* **2010**, *122*, 1682; c) Y. Shibata, K. Noguchi, K. Tanaka, *Org. Lett.* **2010**, *12*, 5596.

[5] a) X.-Z. Shu, S. Huang, D. Shu, I. A. Guzei, W. Tang, *Angew. Chem. Int. Ed.* **2011**, *50*, 8153; *Angew. Chem.* **2011**, *123*, 8303; b) X.-Z. Shu, X. Li, D. Shu, S. Huang, C. M. Schienebeck, X. Zhou, P. J. Robichaux, W. Tang, *J. Am. Chem. Soc.* **2012**, *134*, 5211; c) X.-Z. Shu, C. M. Schienebeck, W. Song, I. A. Guzei, W. Tang, *Angew. Chem. Int. Ed.* **2013**, *52*, 13601; *Angew. Chem.* **2013**, *125*, 13846; d) X. Xu, P. Liu, X.-Z. Shu, W. Tang, K. N. Houk, *J. Am. Chem. Soc.* **2013**, *135*, 9271.

[6] a) Y. Shibata, K. Noguchi, K. Tanaka, *J. Am. Chem. Soc.* **2010**, *132*, 7896; b) C. Brancour, T. Fukuyama, Y. Ohta, I. Ryu, A. L. Dhimane, L. Fensterbank, M. Malacria, *Chem. Commun.* **2010**, *46*, 5470; c) T. Fukuyama, Y. Ohta, C. Brancour, K. Miyagawa, I. Ryu, A.-L. Dhimane, L. Fensterbank, M. Malacria, *Chem. Eur. J.* **2012**, *18*, 7243.

[7] X.-Z. Shu, D. Shu, C. M. Schienebeck, W. Tang, *Chem. Soc. Rev.* **2012**, *41*, 7698.

[8] X. Li, W. Song, W. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 16797.

[9] T. Haven, G. Kubik, S. Haubenreisser, M. Niggemann, *Angew. Chem. Int. Ed.* **2013**, *52*, 4016; *Angew. Chem.* **2013**, *125*, 4108.

[10] For selected reviews on the bioactivity of indoles, see: a) S.-M. Li, *Nat. Prod. Rep.* **2010**, *27*, 57; b) N. A. S. Ali, B. A. Dar, V. Pradhan, M. Farooqui, *Mini-Rev. Med. Chem.* **2013**, *13*, 1792; c) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules* **2013**, *18*, 6620.

[11] For selected reviews on indole synthesis, see: a) J. Barluenga, F. Rodriguez, F. J. Fananas, *Chem. Asian J.* **2009**, *4*, 1036; b) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195; c) R. Vicente, *Org. Biomol. Chem.* **2011**, *9*, 6469; d) M. Platon, R. Amardeil, L. Djakovitch, J.-C. Hierso, *Chem. Soc. Rev.* **2012**, *41*, 3929.

[12] a) P. Kothandaraman, W. Rao, S. J. Foo, P. W. H. Chan, *Angew. Chem. Int. Ed.* **2010**, *49*, 4619; *Angew. Chem.* **2010**, *122*, 4723; b) P. Kothandaraman, S. R. Mothe, S. S. M. Toh, P. W. H. Chan, *J. Org. Chem.* **2011**, *76*, 7633; c) D. Susanti, F. Koh, J. A. Kusuma, P. Kothandaraman, P. W. H. Chan, *J. Org. Chem.* **2012**, *77*, 7166; d) P. Kothandaraman, B. Q. Koh, T. Limpanuparb, H. Hirao, P. W. H. Chan, *Chem. Eur. J.* **2013**, *19*, 1978.

[13] H. Li, X. Li, H.-Y. Wang, G. N. Winston-McPherson, H.-m. J. Geng, I. A. Guzei, W. Tang, *Chem. Commun.* **2014**, *50*, 12293.

[14] a) T. L. Holton, H. Shechter, *J. Org. Chem.* **1995**, *60*, 4725; b) M. McGuiness, H. Shechter, *Tetrahedron Lett.* **2002**, *43*, 8425; c) M. I. Javed, M. Brewer, *Org. Lett.* **2007**, *9*, 1789; d) D. C. Moebius, J. S. Kingsbury, *J. Am. Chem. Soc.* **2009**, *131*, 878.

[15] For selected reviews on cyclopropanations, see: a) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977; b) H. Y. Kim, P. J. Walsh, *Acc. Chem. Res.* **2012**, *45*, 1533; c) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Synthesis* **2014**, 979.

[16] For selected reviews on the importance and utility of cyclopropanes, see: a) H. U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151; b) M. Nakamura, H. Isobe, E. Nakamura, *Chem. Rev.* **2003**, *103*, 1295; c) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117; d) D. Y. K. Chen, R. H. Pouwer, J.-A. Richard, *Chem. Soc. Rev.* **2012**, *41*, 4631; e) P. Tang, Y. Qin, *Synthesis* **2012**, 2969; f) D. J. Mack, J. T. Njardarson, *ACS Catal.* **2013**, *3*, 272; g) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5504; *Angew. Chem.* **2014**, *126*, 5608; h) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804; i) H. K. Grover, M. R. Emmett, M. A. Kerr, *Org. Biomol. Chem.* **2015**, *13*, 655.

[17] a) X. Han, H. Li, R. P. Hughes, J. Wu, *Angew. Chem. Int. Ed.* **2012**, *51*, 10390; *Angew. Chem.* **2012**, *124*, 10536; b) D. Shu, W. Song, X. Li, W. Tang, *Angew. Chem. Int. Ed.* **2013**, *52*, 3237; *Angew. Chem.* **2013**, *125*, 3319.

[18] a) A. Shafiee, A. Ahond, A. M. Bui, Y. Langlois, C. Riche, P. Potier, *Tetrahedron Lett.* **1976**, *17*, 921; b) M. Andriantsiferana, R. Besselievre, C. Riche, H. P. Husson, *Tetrahedron Lett.* **1977**, *18*, 2587; c) A. R. Carroll, E. Hyde, J. Smith, R. J. Quinn, G. Guymer, P. I. Forster, *J. Org. Chem.* **2005**, *70*, 1096; d) T. Taniguchi, C. L. Martin, K. Monde, K. Nakanishi, N. Berova, L. E. Overman, *J. Nat. Prod.* **2009**, *72*, 430.

[19] a) A. D. Napper, J. Hixon, T. McDonagh, K. Keavey, J. F. Pons, J. Barker, W. T. Yau, P. Amouzegh, A. Flegg, E. Hamelin, R. J. Thomas, M. Kates, S. Jones, M. A. Navia, J. Saunders, P. S. DiStefano, R. Curtis, *J. Med. Chem.* **2005**, *48*, 8045; b) T. Barf, F. Lehmann, K. Hammer, S. Haile, E. Axen, C. Medina, J. Uppenberg, S. Svensson, L. Rondahl, T. Lundbaeck, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1745; c) E. Yamuna, R. A. Kumar, M. Zeller, K. J. R. Prasad, *Eur. J. Med. Chem.* **2012**, *47*, 228.

[20] a) A. Del Zotto, W. Baratta, G. Verardo, P. Rigo, *Eur. J. Org. Chem.* **2000**, 2795; b) D. M. Hodgson, D. Angrish, *Chem. Eur. J.* **2007**, *13*, 3470; c) C. Vovard-Le Bray, S. Derien, P. H. Dixneuf, *Angew. Chem. Int. Ed.* **2009**, *48*, 1439; *Angew. Chem.* **2009**, *121*, 1467.

[21] M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002.

[22] CCDC 1042160 (**8f**), 1042158 ((*E*)-**16b**), and 1042159 ((*Z*)-**16b**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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