Enantioselective Cycloaddition

DOI: 10.1002/anie.201105815

Enantioselective Gold(I)-Catalyzed Intramolecular (4+3) Cycloadditions of Allenedienes**

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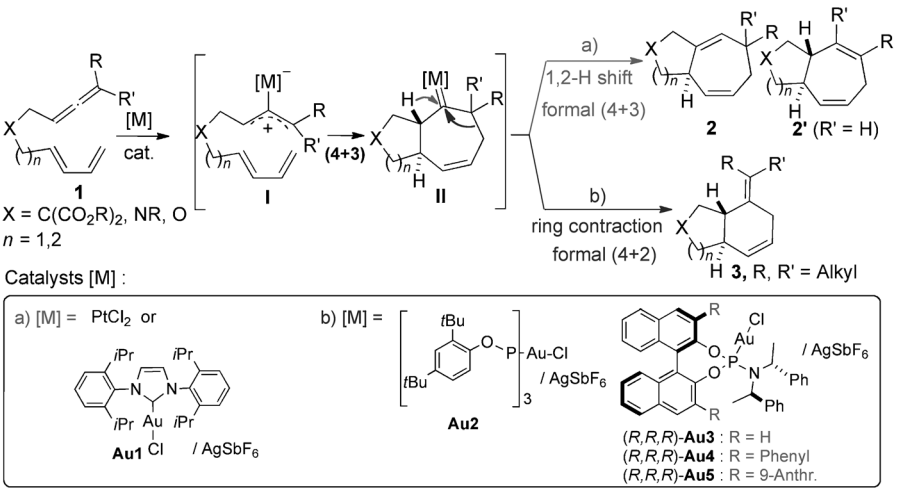
The (4+3) cycloaddition of conjugated dienes and allylic cations represents a highly valuable strategy for the preparation of seven-membered carbocycles.[1] Indeed, this type of annulation has been successfully used as a key step in the synthesis of several complex natural products and advanced intermediates.[2,3] However, very important challenges, such as the development of catalytic versions that work with readily available precursors,[4] and principally, the implementation of enantioselective variants, remain to be satisfactorily developed. Indeed, we are aware of only two isolated reports on catalytic enantioselective (4+3) cycloadditions of allylic cations, and both deal with the intermolecular annulation of furans.[5–7]



Scheme 1. Pt- and Au-catalyzed cycloadditions of allenedienes **1**.[8,10a]

We have recently reported a new type of (4+3) cycloaddition strategy based on the platinum- or gold-catalyzed intramolecular reaction of allene-tethered dienes such as **1** (Scheme 1). The reaction is particularly efficient when catalyzed by the cationic gold(I) complex **Au1**/$AgSbF_6$, which features a σ-donating N-heterocyclic carbene ligand.[8,9] In the course of these studies, we also discovered that allenedienes **1**, when dialkylated at the distal position of the allene (R, R′ = alkyl), preferentially provide (4+2) cycloadducts of type **3**, as long as the gold catalyst incorporates a π-acidic ligand such as a phosphite or a phosphoramidite.[10,8b] Additionally, we have found that when using suitable chiral phosphoramidite/gold(I) catalysts (e.g. (*R*,*R*,*R*)-**Au3**–**Au5**) the cycloadditions proceed in an enantioselective manner to provide optically active bicyclic compounds **3**.[10a,11] Mechanistic studies suggest that both types of products, **2** and **3**, arise from the common carbenic species **II**,[12] itself coming from the (4+3) cycloaddition of **1** via allylic cation intermediate **I** (Scheme 1). Species **II** might then evolve either by ring contraction (1,2-alkyl migration, route b) or by a standard 1,2-H shift (route a).[13] Although the phosphite type of ligands seem to favor the ring contraction process over the 1,2-H shift, theoretical data suggest that the activation barriers for both processes are not so different.[10a,b] Therefore, we reasoned that chiral phosphoramidite/gold catalysts might be also capable of inducing (4+3) annulations, provided that the ring-contraction route (route b) could be slightly deactivated. Herein, we demonstrate the viability of this approach by reporting a highly enantioselective intramolecular (4+3) cycloaddition of allenedienes **1**. The reactions are promoted by the chiral phosphoramidite/gold(I) catalyst (*R*,*R*,*R*)-**Au5**/$AgSbF_6$ and provide a straightforward route to optically active, synthetically relevant bicyclo[5.3.0]decadiene and bicyclo[5.4.0]undecadiene skeletons. To the best of our knowledge the transformation represents the first example of an intramolecular, highly enantioselective (4C + 3C) cycloaddition.

Previous studies in the group suggested that reducing the number of substituents at the allene terminus of **1** (from two to one) has a drastic negative effect on the formation of cyclohexene adducts **3**, while cycloheptenyl products **2** and **2'** can still be satisfactorily obtained.[14] Therefore, we initially

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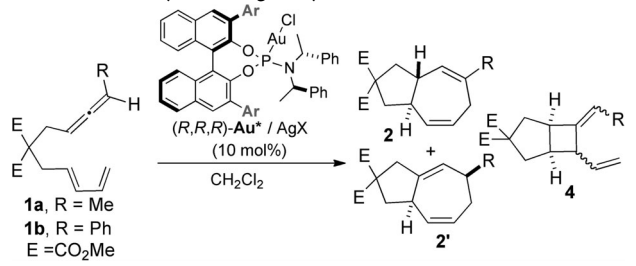
[**] This work was supported by the Spanish MEC (SAF2007-61015, SAF2010-20822-C02, Consolider Ingenio 2010 CSD2007-00006), the ERDF and the Xunta de Galicia INCITE09 209 084PR, GRC2010/12. H.F. acknowledges Fundação para a Ciência e a Tecnologia-Portugal for a PhD Grant SFRH/BD/60214/2009.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201105815.

checked the performance of monosubstituted allenediene **1a** (R = Me, R′ = H, X = $C(CO_2Me)_2$) in the presence of several chiral phosphoramidite/gold catalysts (Table 1). Gratifyingly,

Table 1: Preliminary screening on cycloadditions of **1a–b**.[a,b]



Entry	1	AgX	Au*	t [h]	Products (ratio)[c]	Yield [%][d]	ee (2) [%][e]
1	**1a**	$AgSbF_6$	**Au5**	4	**2a**/**2a′**/**4a** (3:2:1)	55	–[f]
2	**1a**	$AgSbF_6$	**Au2**	0.5	**4a**[g]	40[h]	–
3	**1b**	$AgSbF_6$	**Au5**	8	**2b**/**2b′** (8:1)	74	87
4	**1b**	$AgSbF_6$	**Au6**[i]	5	**2b**/**2b′**/**4b** (1:1:1)	69[j]	85
5	**1b**	$AgSbF_6$	**Au3**	17	**2b**/**2b′** (2:1)	70	13
6	**1b**	$AgSbF_6$	**Au4**	5	**2b**/**2b′** (4:1)	75	40
7	**1b**	$AgBF_4$	**Au5**	48	**2b**/**2b′** (1:0)	46	81
8	**1b**	$AgNTf_2$	**Au5**	36	**2b**/**2b′** (13:1)	64	84
9	**1b**	AgOTf	**Au5**	35	**2b**/**2b′** (15:1)	10	84
10	**1b**	AgOTs	**Au5**	–	–	–[k]	–
11[l]	**1b**	$AgSbF_6$	**Au5**	11	**2b**/**2b′** (9:1)	64	87
12[m]	**1b**	$AgSbF_6$	**Au5**	14	**2b**/**2b′** (9:1)	56	85

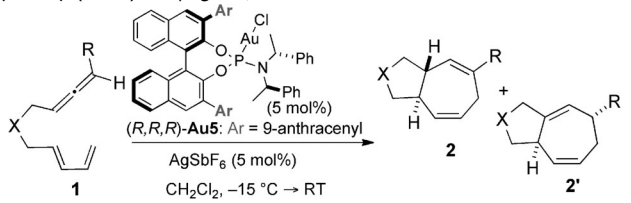
[a] Allenediene **1** (1 equiv) was added to a mixture of AgX (10 mol%) and (*R*,*R*,*R*)-**Au*** (10 mol%), in CH_2Cl_2 (0.1 M) at −15 °C and the mixture was slowly warmed to RT. [b] Conversions are greater than 99%, as determined by ^{1}H NMR spectroscopy, unless otherwise noted. [c] Determined by ^{1}H NMR spectroscopy of the crude mixtures. [d] Combined yield of **2** and **2′** upon isolation unless otherwise noted. [e] Determined by HPLC. [f] The *ee* value was not determined. [g] Result taken from reference [10a]: **4a** was observed together with other unknown products. [h] Yield of **4a** as determined by GC analysis. [i] **Au6**: Ar = 9-phenanthryl. [j] Combined yield of **2b**, **2b′**, and **4b**. [k] 0% conversion; **1b** was recovered after 24 h. [l] Used 5 mol% of (*R*,*R*,*R*)-**Au5**/$AgSbF_6$. [m] Used 2 mol% of (*R*,*R*,*R*)-**Au5**/$AgSbF_6$.

treatment of this substrate with (*R*,*R*,*R*)-**Au5**/$AgSbF_6$ (10 mol%), provided the (4+3) cycloadducts **2a** and **2a′** (3:2 ratio), together with a lower quantity of the (2+2) adduct **4a**, in an 55% combined yield (Table 1, entry 1).[15] Interestingly, the racemic phosphite/gold catalyst **Au2**/$AgSbF_6$ affords a more complex mixture of products than the above phosphoramidite catalyst (Table 1, entry 2).[10a] Pleasingly, the cycloaddition of the related allenediene **1b**, which bears a phenyl group at the allene terminus, was completely selective, thus providing the (4+3) cycloadducts **2b** and **2b′** in a 8:1 ratio and a good 74% combined yield (Table 1, entry 3). Importantly, analysis of the enantioselectivity of this reaction revealed that **2b** was obtained in 87% *ee*,[16] thus confirming the potential of this phosphoramidite/gold catalyst to induce high levels of asymmetry in these (4+3) cycloadditions.

As is shown in Table 1 (Table 1, entries 3–6), precatalyst (*R*,*R*,*R*)-**Au5**, which bears 9-anthracenyl groups at the 3 and 3′ positions of the binaphthol unit, provided the best selectivity in favor of the (4+3) adducts, as well as the highest *ee* values. A related phenanthryl-derived complex (*R*,*R*,*R*)-**Au6** also provided the (4+3) adducts **2b** and **2b′** with a good 85% *ee*, however, the reaction also gave a considerable amount of the (2+2) cycloadduct **4b** (Table 1, entry 4).[17] Other precatalysts, such as the phenyl-derived complex (*R*,*R*,*R*)-**Au4** and the 3,3′ nonsubstituted catalyst (*R*,*R*,*R*)-**Au3**, led to much lower *ee* values (Table 1, entries 5 and 6). The counterion seems to have little effect on the enantioselectivity (Table 1, entries 7–10). Thus, an equimolar combination of $AgSbF_6$ and (*R*,*R*,*R*)-**Au5** turned out to be the optimum catalyst. Importantly, reduction of the catalyst loading to 5 mol%, and even 2 mol%, did not affect the enantioselectivity, although the transformation requires longer reaction times and leads to slightly lower yields (Table 1, entries 11 and 12).[18]

Once an optimum catalytic system had been established, we evaluated the versatility and scope of the process, typically using 5 mol% of (*R*,*R*,*R*)-**Au5**/$AgSbF_6$. As shown in the Table 2, allenediene **1c**, with an electron-donating *ortho*-methoxy substituent on the aryl group of the allene, also participated in the cycloaddition, thus providing the (4+3) cycloadducts **2c**/**2c′** in 91% yield and 88% *ee* (Table 2, entry 2). In contrast, electron-withdrawing substituents on the aromatic ring, such as a *para*-trifluoromethyl group, were not tolerated, thus leading to complete recovery of the starting material (Table 2, entry 3). The presence of the

Table 2: Enantioselective (4+3) cycloadditions of allenedienes **1**, catalyzed by (*R*,*R*,*R*)-**Au5**/$AgSbF_6$.[a,b]



Entry	1	R	X	2/2′[c]	Yield [%][d]	ee (2) [%]
1	**1b**	C_6H_5	$C(CO_2Me)_2$	9 :1	64	87
2	**1c**	2-$OMeC_6H_4$	$C(CO_2Me)_2$	3.5:1	91	88[e]
3	**1d**	4-$F_3CC_6H_4$	$C(CO_2Me)_2$	–	–[f]	–
4	**1e**	C_6H_5	NTs	1:0	74	95
5	**1f**	2-MeC_6H_4	NTs	1:0	68	95
6	**1g**	3-MeC_6H_4	NTs	1:0	75	95
7	**1h**	2-$OMeC_6H_4$	NTs	1:0	80	98

[a] Allenediene **1** (1 equiv) was added to a mixture of $AgSbF_6$ (5 mol%) and (*R*,*R*,*R*)-**Au5** (5 mol%), in CH_2Cl_2 (0.1 M) at −15 °C and the mixture slowly warmed to RT. [b] Conversions are greater than 99%, as determined by ^{1}H NMR spectroscopy, unless otherwise noted. [c] Determined by ^{1}H NMR spectroscopy of the crude mixtures. [d] Combined yield of **2** and **2′** upon isolation. [e] Used 10 mol% of catalyst. [f] **1d** was recovered after 24 h at RT.

geminal diester in the connecting chain of **1** is not essential. Thus, the reaction of *N*-tosyl derivative **1e** provided the (4+3) cycloadduct **2e** in 74% yield, with complete regioselectivity and with an excellent 95% *ee* (Table 2, entry 4). Also, the *ortho*-methyl and *meta*-methyl derivatives **1f** and **1g** provided the corresponding adducts **2f** and **2g** with good yields and 95% *ee* (Table 2, entries 5 and 6). The cycloaddition of *ortho*-methoxy-substituted derivative **1h** provided even better enantioselectivity, and adduct **2h** was isolated in 80% yield and 98% *ee* (Table 2, entry 7).[19]

Interestingly, while disubstitution at the allene terminus favors the formation of (4+2) cycloadducts **3**,[10a] introduction of a third substituent at the internal position instead of the terminal position of the allene, results in the generation of cycloheptenyl products **2**. Therefore, treatment of the 1,3-dimethyl-substituted allenediene **1i** under the standard conditions ((*R*,*R*,*R*)-**Au5**/$AgSbF_6$) yielded the (4+3) adduct **2i** with complete regioselectivity, 78% yield and an excellent 95% *ee* (Table 3, entry 1). The structure of the product, which features a quaternary bridgehead carbon, was unambiguously determined by NMR spectroscopy and X-ray crystallography, which also established the absolute configuration (Figure 1).[20]

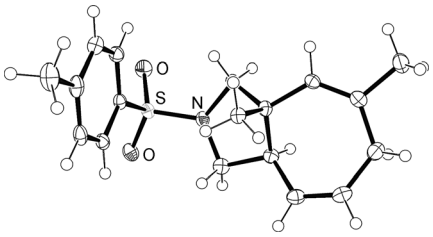


Figure 1. Solid-state molecular structure of (3a*R*, 8a*R*)-**2i**.[20]

(4+3) adduct **2k** (98% *ee*) and an interesting bicyclic product, **5k**, resulting from a new type of formal (4+2) annulation (Table 3, entry 3). The structure and stereochemical configuration of **2k** and **5k** could be determined by NMR spectroscopy and X-ray crystallography (Figure 2).[22] Importantly, both adducts were obtained with almost the same enantioselectivity (±2% *ee*), thus suggesting that they could arise from a common intermediate. Indeed, the formation of **5k** can be rationalized in terms of 1,2 migration of the bridgehead tertiary carbon atom on a 5,7-cycloheptyl gold carbene intermediate such as **II** (Scheme 1). This migration entails a ring expansion of the five-membered ring and a concomitant contraction of the seven-membered carbocycle.[23]

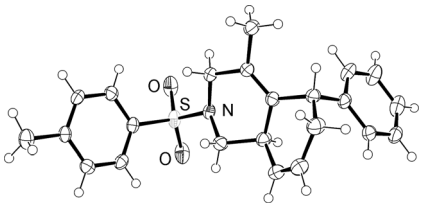
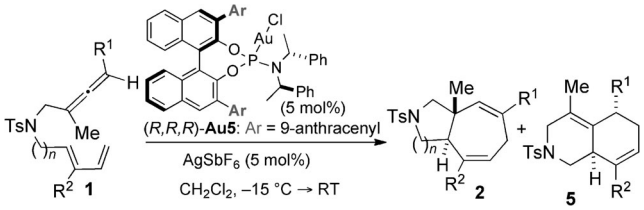


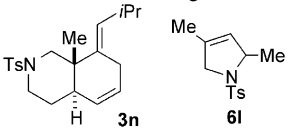
Figure 2. Solid-state molecular structure of **5k**.[22]

Table 3: Enantioselective (4+3) cycloadditions of other allenedienes **1**.[a,b]



Entry	**1**	*n*	R^1	R^2	**2**/**5**	Yield [%][c]	*ee* (**2**) [%]
1	**1i**	1	Me	H	1:0	78	95
2	**1j**	1	*i*Pr	H	1:0	76	95
3	**1k**	1	C_6H_5	H	4:6	82[d]	98[e]
4	**1l**	1	Me	Me	1:1[f]	80[g]	93
5	**1m**	2	Me	H	1:0	95	98
6	**1n**	2	*i*Pr	H	1:0[h]	95[i]	95

[a] Allenediene **1** (1 equiv) was added to a mixture of $AgSbF_6$ (5 mol%) and (*R*,*R*,*R*)-**Au5** (5 mol%), in CH_2Cl_2 (0.1 M) at −15 °C and slowly warmed to RT. [b] Conversions are greater than 99%, as determined by ^{1}H NMR spectroscopy, unless otherwise noted. [c] Yields are of isolated **2**, unless otherwise noted. [d] Combined yield of **2k** and **5k**. [e] The *ee* value of **2k**; the *ee* value of **5k** is 96%; [f] Ratio of **2l**/**6l**/**5l** = 1:2:1. [g] Combined yield of **2l**, **5l**, and **6l**. [h] A small amount (<10%) of **3n** was also obtained together with **2n**.[21] [i] Combined yield of **2n** and **3n**.



Allenediene **1j**, which also contains a methyl substituent at the internal allenic position, provided the corresponding (4+3) product **2j** with good yield and 95% *ee* (Table 3, entry 2). Curiously, allenediene **1k**, with a phenyl group at the allene terminus, reacted to give a 4:6 mixture of the expected

The cycloaddition of allenedienes bearing alkyl substituents at the diene, such as **1l**, can also be achieved with high *ee*. However, in addition to the desired (4+3) adduct **2l** (93% *ee*), the reaction also gave the 6,6-bicyclic product **5l**, and a second side product **6l**, which must arise from the rupture of the allenediene and a subsequent intramolecular hydroamination reaction (Table 3, entry 4).[24]

Finally, the cycloaddition of allenedienes **1m** and **1n**, which feature a longer connecting chain between the allene and the diene, proceeded efficiently, thus providing the corresponding cycloadducts with good yields and excellent *ee* values (Table 3, entries 5 and 6). Moreover, the structure **2m** could be resolved by X-ray crystallography, thus confirming the absolute stereochemistry of the major enantiomer (Figure 3).[25] Overall, these results demonstrate that the method constitutes an efficient asymmetric approach to enantiopure 5,7- and 6,7-fused bicyclic systems with a quaternary stereocenter at the ring fusion.

In summary, we have described the first examples of a catalytic and highly enantioselective intramolecular (4C+3C) cycloaddition reaction. This method leads to synthetically appealing bicyclo[5.3.0]decadiene and bicyclo-

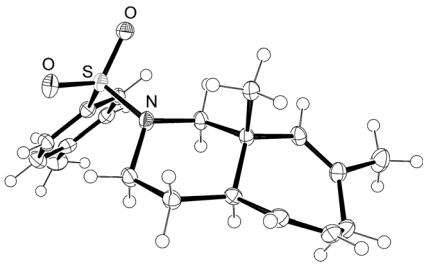


Figure 3. Solid-state molecular structure of (4a*R*, 9a*S*)-**2m**.[25]

[5.4.0]undecadiene skeletons with good yields, complete diastereocontrol, and excellent enantioselectivities. The atom economy and stereoselectivity of the process, together with its operational simplicity, allows this method to be ranked among the most practical alternatives to make optically active 5,7-and 6,7-fused bicyclic systems.

Received: August 17, 2011
Published online: October 13, 2011

Keywords: allenes · cycloaddition · enantioselectivity · gold · homogeneous catalysis

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[11] For more recent related work with other phosphoramidite/gold catalysts, see: a) A. Z. González, F. D. Toste, *Org. Lett.* **2010**, *12*, 200–203; b) H. Teller, S. Flugge, R. Goddard, A. Fürstner, *Angew. Chem.* **2010**, *122*, 1993–1997; *Angew. Chem. Int. Ed.* **2010**, *49*, 1949–1953.

[12] This gold(I) carbene intermediate **II** can also be understood as a gold(I)-stabilized carbocation. The degree of carbenic character depends on the nature of the ligands on gold: a) D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. M. Wang, W. A. Goddard, F. D. Toste, *Nat. Chem.* **2009**, *1*, 482–486; b) G. Seidel, R. Mynott, A. Fürstner, *Angew. Chem.* **2009**, *121*, 2548–2551; *Angew. Chem. Int. Ed.* **2009**, *48*, 2510–2513.

[13] It has been shown that disubstitution at the allene terminus and π-acidic ligands on gold, the latter enhancing the zwitterionic character of **II**, favor the ring contraction (1,2-alkyl shift) to give the (4+2) adducts **3**. Conversely, the use of $PtCl_2$ or σ-donating ligands on gold favor the 1,2-H shift to give the (4+3) adducts **2** and/or **2′**.[8–10]

[14] Indeed, bicyclic compounds such as **3** are only efficiently obtained from allenedienes with two alkyl substitutents at the allene terminus.[10,11,9a,b]

[15] The formation of the (2+2) cycloadduct **4a** can be explained in terms of a cationic stepwise pathway as suggested in related Au-catalyzed (2+2) cycloadditions of allene-tethered alkenes, see: a) M. R. Luzung, P. Mauleón, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 12402–12403; for a related recent work, see: b) A. Z.

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[16] Cycloadducts **2b** and **2b′** are obtained with the same enantioselectivity, in consonance with the mechanistic pathway shown in Scheme 1.

[17] The yields and selectivities provided by (*R*,*R*,*R*)-**Au6**/$AgSbF_6$ in the (4+2) cycloaddition of allenedienes disubstituted at the allene distal position are typically similar to those provided by (*R*,*R*,*R*)-**Au5**/$AgSbF_6$ (unpublished results).

[18] Allenediene **1b** slowly polymerizes even at low temperatures. Therefore, long reactions times should be avoided.

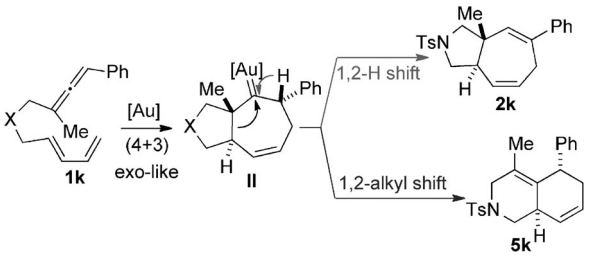
[19] Cycloadduct **2h** was characterized by X-ray crystallography; CCDC 836785 (**2h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[20] CCDC 836784 (**2i**) contains 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.

[21] **3n** could not be separated from **2n** by column chromatography on silica gel. The identification of **3n** as a side product was confirmed by its independent preparation, which allowed us to obtain suitable crystals for X-ray crystallography. CCDC 836787 (**3n**) contains 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.

[22] The absolute stereochemistry of **5k** was unambiguously determined by X-ray crystallography. CCDC 836788 (**5k**) contains 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.

[23] Mechanistic rational for the formation of **2k** and **5k** from the same reactive intermediate **II**:



[24] See details in the Supporting Information. For a review on intramolecular hydroamination reactions of allenes, see: R. A. Widenhoefer, X. Han, *Eur. J. Org. Chem.* **2006**, 4555 – 4563.

[25] CCDC 836786 (**2m**) contains 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.

