CHEMISTRY
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To be cited as: *Chem. Eur. J.* 10.1002/chem.201801031

Link to VoR: http://dx.doi.org/10.1002/chem.201801031

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Different Selectivities in the Insertions into C(sp^2)-H Bonds – Benzofulvenes by Dual Gold Catalysis Competition Experiments**

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[**] D. M. Lustosa was supported by the Brazilian Council for Scientific and Technological Development (CNPq, Science without Borders Program, 2015–2018)

Keywords: dual gold catalysis, gold vinylidenes, C,H insertion, benzofulvenes, chemoselectivity

Abstract: An unprecedented, often almost quantitative access to tricyclic aromatic compounds by dual gold catalysis was developed. This synthetic route expands the scope of benzofulvene derivatives through a C(sp^2)-H bond insertion in easily available starting materials. The insertion takes place with an exclusive chemoselectivity with respect to the competing aromatic C-H positions. A bidirectional synthesis with two competing ortho-aryl C,H bonds in the selectivity-determining step also shows perfect selectivity; this result is explained by a computational investigation of the two

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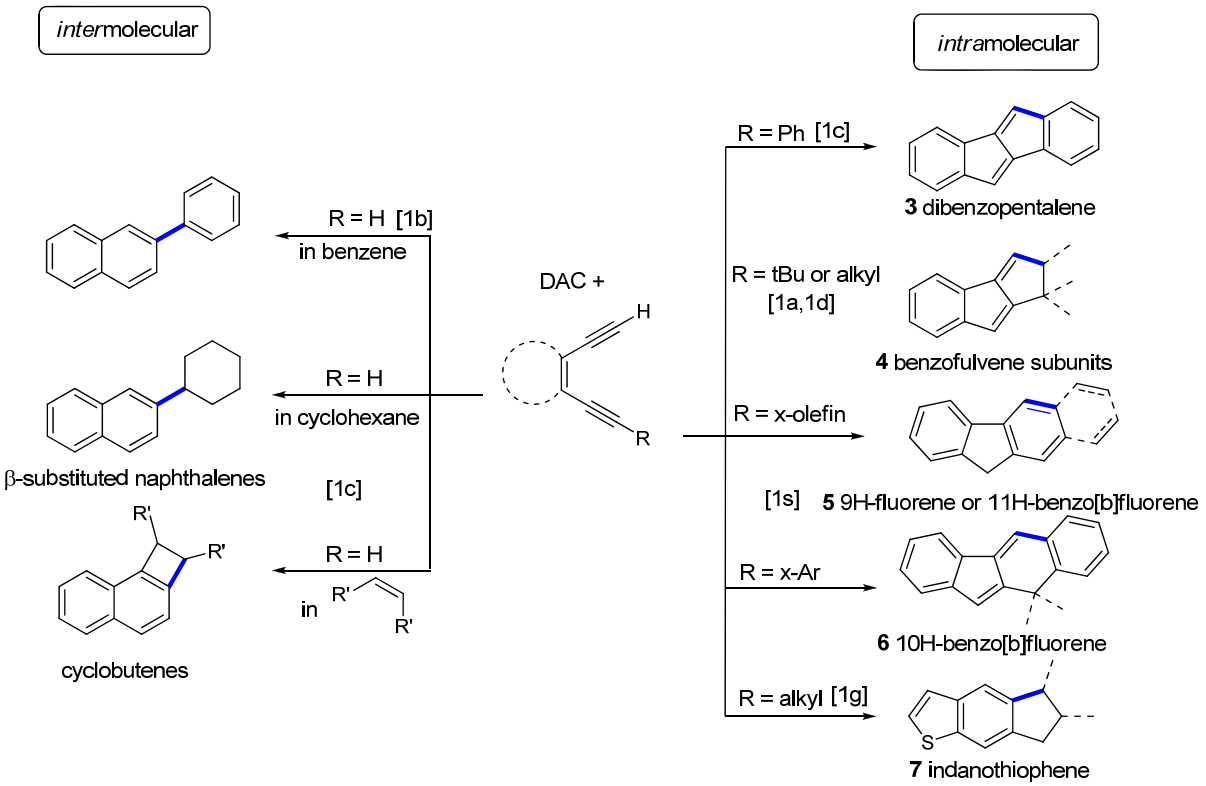
conceivable intermediates. The intramolecular competition of two non-equivalent aryl-C,H bond with a benzylic methyl group also showed perfect selectivity.

Introduction

Recently, the field of 1,5-diyne cyclizations by dual[1] gold catalysis[2] has developed substantially.

The synthetic utility of this methodology was already demonstrated by the syntheses of benzofulvenes,[1a,1c,1j] dibenzopentalenes,[1c,1m] benzocyclobutenes[1e] and various annulated aromatic compounds that were derived from either intra- or intermolecular C-H insertions[1b, 1o,1p] (Scheme 1). The insertion step is initated by an gold vinylidene intermediate formed in situ by a 5-*exo*-*dig* cyclization, a species for which a derivate has been recently characterized spectroscopically by Widenhoefer *et al*. [3] As an alternative to the vinylidene intermediate, depending on the backbone and the substitution pattern of the substrate, a 6-*endo*-*dig* cyclization can take place, leading to digold-substituted carbene species as key intermediates.[1g,1h,1n] A subsequent C,H insertion of these high energy intermediates enables the activation of unreactive sp^2- and sp^3-C,H bonds.



Scheme 1. Scope of dual catalysis.

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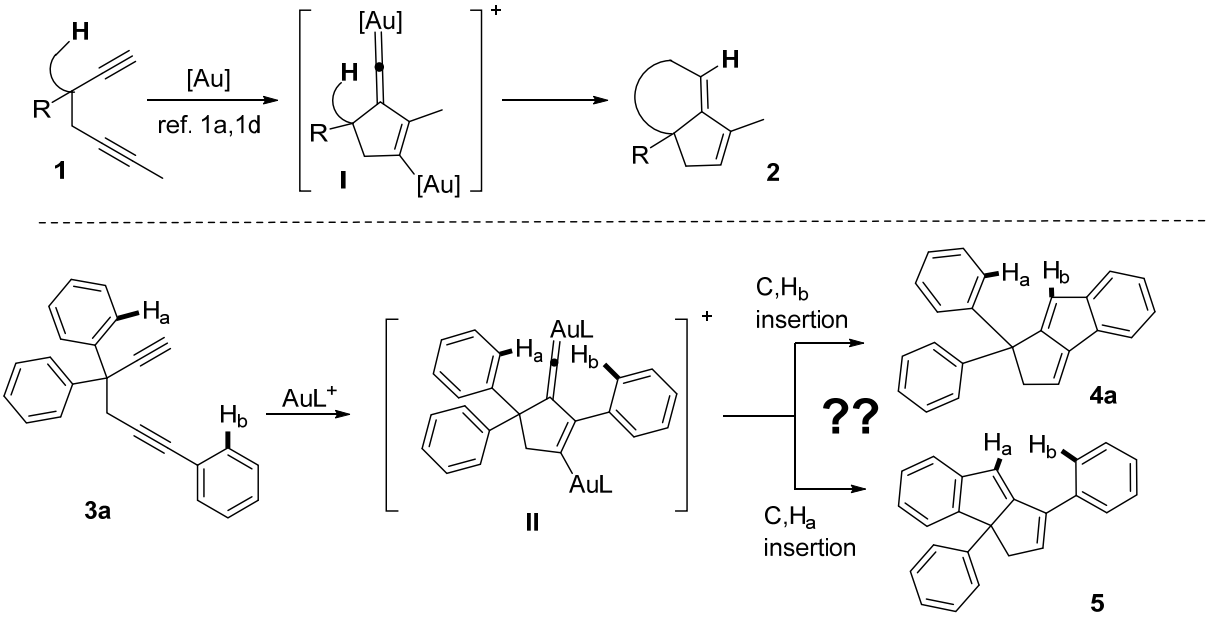
Based on these principles, dual gold-catalyzed cyclizations represent a broadly applicable, atom economical[4] and fast access to polycyclic frameworks under mild conditions and with high yields. So far, catalytic approaches to benzofulvenes are based on insertions into the C(sp^3)-H bond of a distal terminal alkyl chain on one of the alkynes.[1a,1d] We now considered a different synthetic strategy in which the intermediate vinylidene is no longer annulated, but it forms the benzannulation in the consecutive insertion step. The idea is based on our recent report on the insertion into CH-bonds offered by substituents at the propargylic position of open-chained substrates which possess one terminal alkyne (Scheme 2, upper part).[1l] For these substrates no conformationally pre-orientated starting materials were needed; due to the Thorpe-Ingold effect[5] these open-chained systems readily cyclized and the intermediate vinylidene **I** was trapped by the substituent in propargylic position. For these systems a good selectivity was achieved by using a simple methyl group, which cannot undergo C,H insersion as a strained four-membered ring would be formed, as "protecting group" at the internal alkyne. In order to implement the new, alternative benzofulvene synthesis, we now applied related open-chained substrates of type **3a** (Scheme 2, lower part). In **3a** a competing an equidistant sp^2-CH-bond was offered by *via* the arene moiety attached to the internal alkyne. This approach, presupposing a chemoselective attack of the vinylidene species, facilitates an alternative functionalization and represents a conceptionally new synthesis of benzofulvenes.



Scheme 2. Diyne cyclization by dual catalysis and envisioned C-H insertion towards benzofulvene **4a** and possible byproduct **5**.

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Results and Discussion

For our studies the test compound **3a** was synthesized and subjected to 5 mol% IPr-DAC-PF_6 (DAC = dual activation catalyst)[1k] in toluene at 60°C. After 1 hour a clean reaction delivered **4a** in excellent yield and perfect selectivity, no byproduct could be detected. The tricyclic structure and the two untouched germinal phenyl groups were unambiguously confirmed by an X-ray single crystal structure analysis of **4a** (Figure 1).[6]

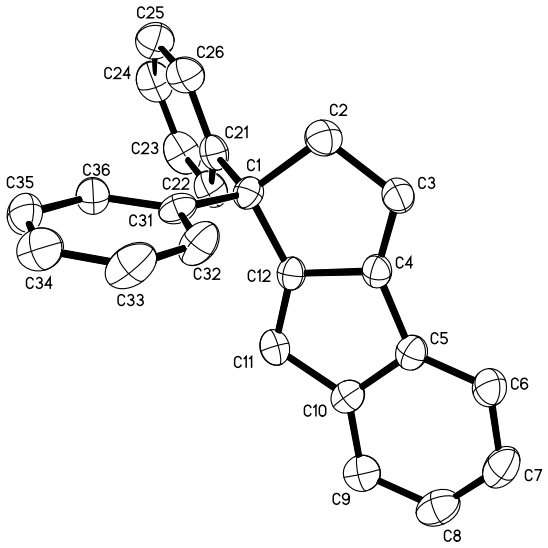

Figure 1. Solid state molecular structure of **4a**. Ellipsoids set at 50% probability. Hydrogen atoms are omitted for clarity.

Next for the conversion of **3a** a variation of the counter ion of the DAC was tested**.** In contrast to our preceding investigation with aliphatic backbones,[1l] an influence of the catalyst's counter ion on the selectivity was observed. While catalysts with $[NTf_2]^-$ and $[PF_6]^-$ showed no byproducts, $[BF_4]^-$ and $[OTf]^-$ gave significant amounts of byproduct. Treatment with DAC-SbF_6 yielded a completely different and fluorescent product, which was very sensitive and could not be isolated. Since DAC-PF_6 showed higher reaction rates than the corresponding catalysts with $[NTf_2]^-$ counter anions, DAC-PF_6 was chosen for the following reactions. The reaction temperature of 60 °C is lower than the temperature needed for the cyclization of substrates of type **1** (80 °C were

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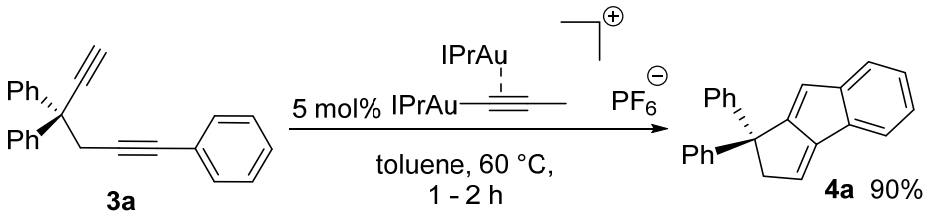
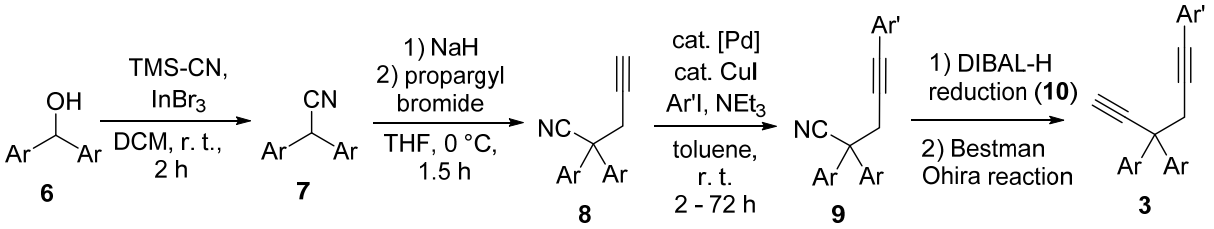
necessary for these compounds). Scheme **3** represents the optimized reaction conditions.



Scheme 3. Conversion of the diyne **3a** under the optimized conditions.

In order to evaluate the scope of the concept, various starting diynes were synthesized, following a strategy depicted in Scheme **4**. Starting point for the synthesis was the generation of a tertiary alcohol **6** by the two-fold Grignard addition to ethyl formate. The alcohol was consecutively transformed to the corresponding nitrile **7** by treatment with trimethylsilyl cyanide via indium(III) bromide catalysis.[7] Propargylation was followed by a Sonogashira coupling with the additional aryl moiety. Then the nitrile group in **9** was transformed to the terminal alkyne **10** by reduction to the corresponding aldehyde with DIBAL-H and subsequent treatment with the Bestmann-Ohira reagent.



Scheme 4. General synthetic route for the preparation of the diynes **3.**

A variety of starting materials was generated in this fashion and then converted to the benzofulvene derivatives. Table **1** summarizes the scope of the catalysis reaction. Overall, up to 99% yield can be obtained with both electron-donating and electron-withdrawing substituents on each of the aromatic moieties attached to the starting diyne systems. The reaction appears to be resilient with respect to electronic influences. Neither substituents on the phenyl groups in the tether nor in the aryl moiety on the alkyne showed a definite trend with respect to the yield. In agreement with previous results, higher reaction rates were observed when the aryl group bearing the attacked C(sp^2)-H bond was functionalized with electron-donating substituents. It is worth mentioning, that in no case a competing insertion *via* the arene in propargylic position took place. This was even not the case for electron-rich moieties at the

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propargylic position in combination which electron-deficient substituents at the internal alkyne part (products **4i**, **4o**, **4q**, **4t**, **4u**).

Table 1. Scope of the synthesis of compounds **4**.

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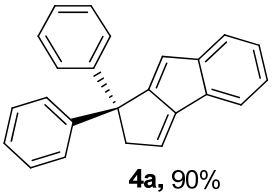
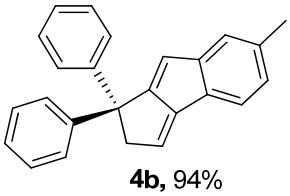
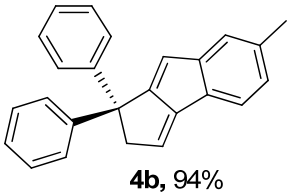


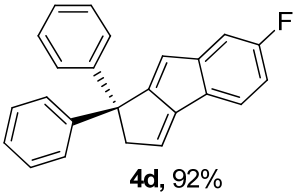
4a, 90%



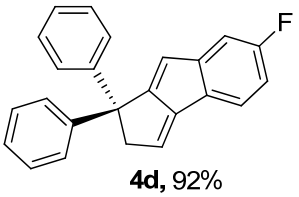
4b, 94%



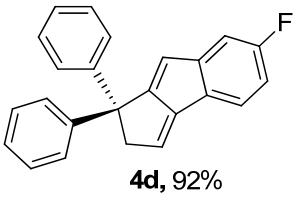
4b, 94%



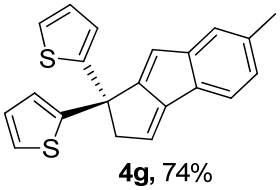
4d, 92%



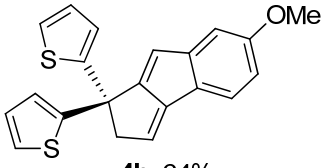
4d, 92%



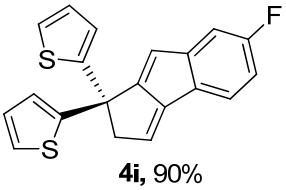
4d, 92%



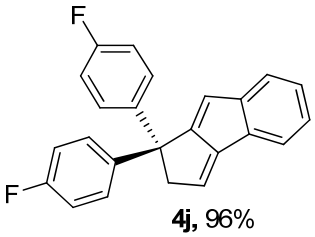
4g, 74%



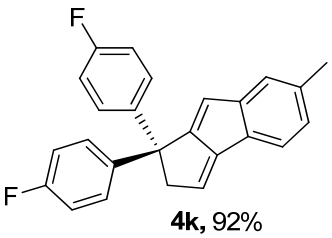
4h, 64%



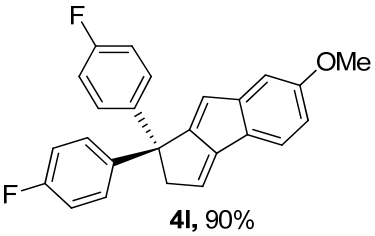
4i, 90%



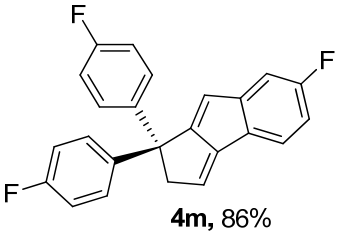
4j, 96%



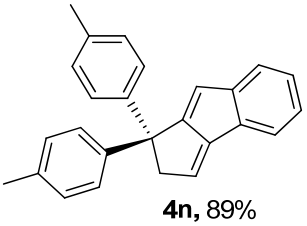
4k, 92%



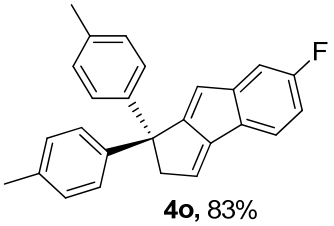
4l, 90%



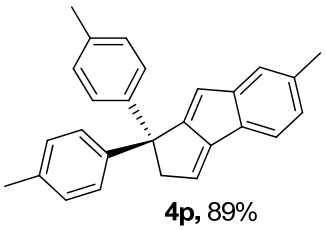
4m, 86%



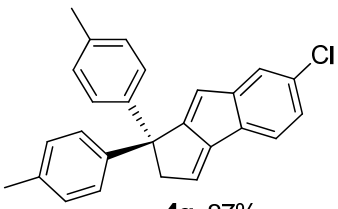
4n, 89%



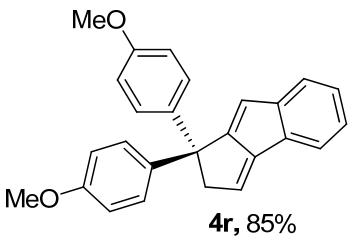
4o, 83%



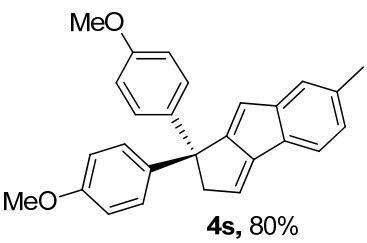
4p, 89%



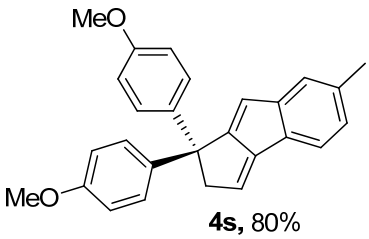
4q, 87%



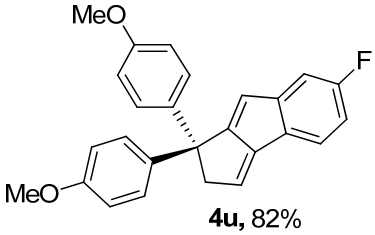
4r, 85%



4s, 80%



4s, 80%



4u, 82%

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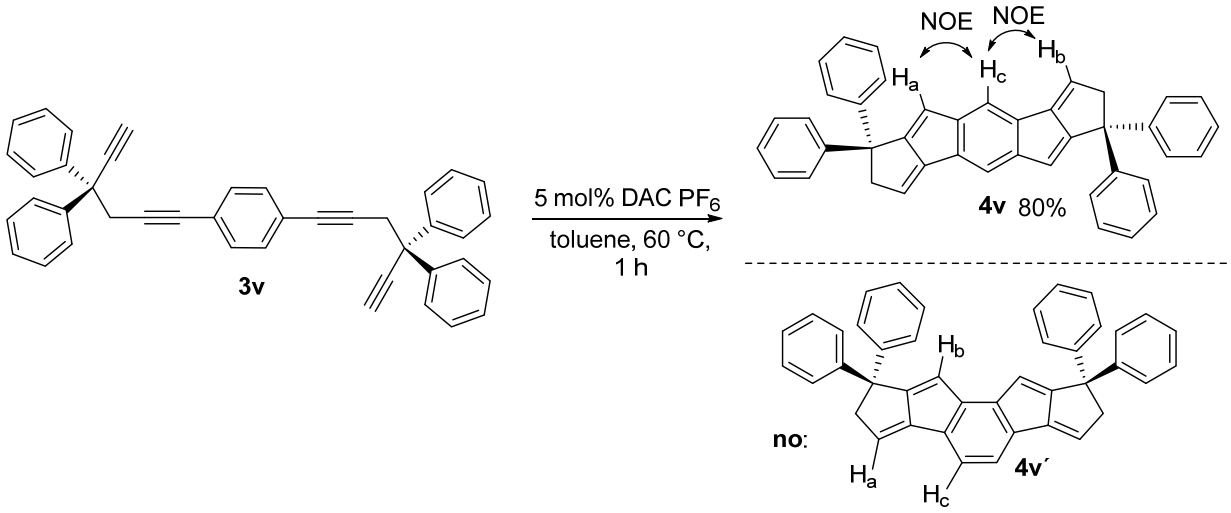
Following this route all benzofulvenes were obtained as the only products in good to very good yields. Compared to the existing approaches, the presented synthetic route enables a range of new substitution patterns.

In order to further examine the synthetic possibilities, a potential substrate for a bidirectional reaction was synthesized (Scheme 5). Using 1,4-diiodobenzene two diyne systems in **3v** were connected.

After the first cyclization, again an intramolecular competition experiment of the two non-equivalent ortho-C,H bonds of the central benzene core is possible. Treatment of the tetrayne system with the gold catalyst delivered the corresponding polycyclic product that precipitated in high yield. The high selectivity of the reaction is remarkable as the formation of two different products **4v** and **4v´** should be possible. As a first structural proof, a NOESY NMR experiment was conducted. It shows cross peaks for both of the fulvene protons H_a and H_b to the central aromatic proton H_c, which clarifies that only the linear annulated product is formed in the reaction. Not even traces of the angular product (here only one NOESY cross peak would be visible) were obtained.



Scheme 5. Bidirectional variant yielding a pentacyclic compound **4v**.

Finally, efforts to grow single crystals of **4v** were successful. The molecular structure is shown in Figure 2, it confirms the linear annulation.

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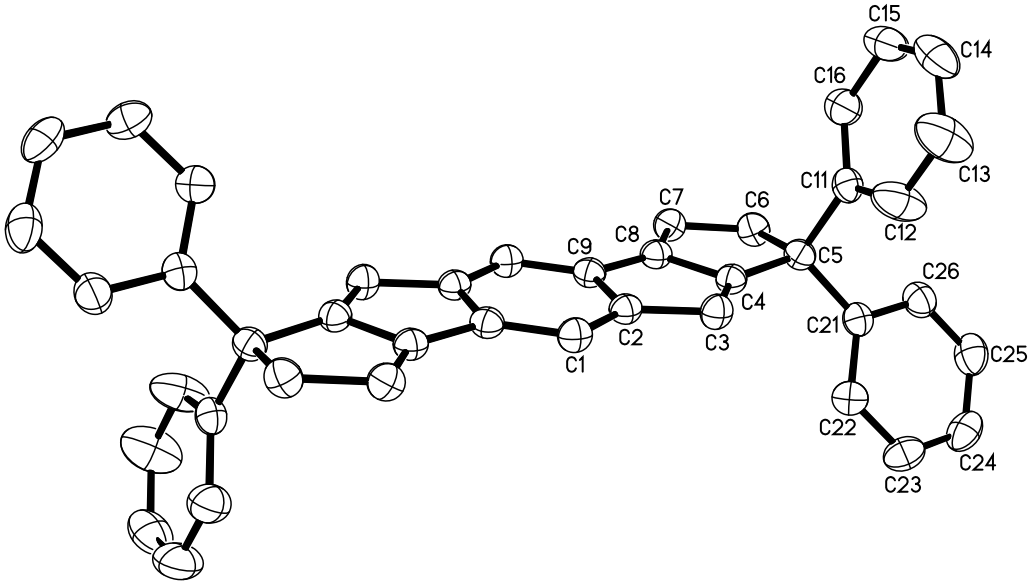
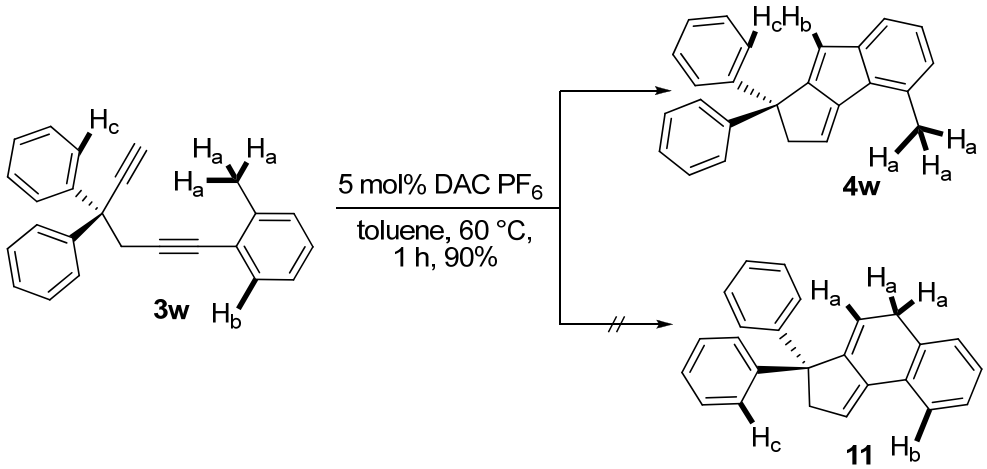


Figure 2. Solid state molecular structure of **4v**. Ellipsoids set at 50% probability. Hydrogen atoms are omitted for clarity.

Furthermore, substrate **3w**, offering three additional benzylic C(sp^3)-H bonds as potentially competing insertion positions, was synthesized. An alternative insertion into the corresponding vinylidene species would deliver a six-membered cycle **11** (Scheme 6). Despite this additional possibility 90% yield of the C(sp^2)-H insertion product **4w** (forming the five-membered system) was obtained as single product. Consequently the methyl group has no apparent influence on the reaction.



Scheme 6. Intramolecular competition experiment with substrate **3w**.

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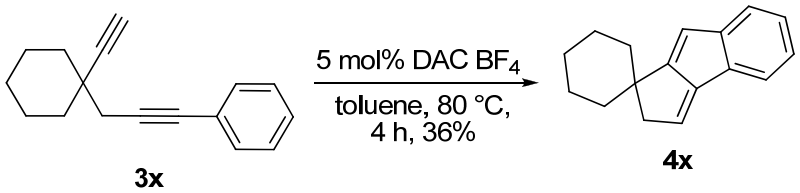
Finally, the diaryl substitutents in propargylic position were replaced by a saturated cyclohexyl framework (Scheme 7, **3x**). Indeed, the spirocyclic benzofulvene derivate **4x** was formed, but despite the increased reaction temperatures and times and a catalyst adaption, the yield of the reaction was only moderate. This behavior probably is caused by the reduced steric demand of the cyclohexyl backbone resulting in a decreased Thorpe-Ingold effect which influences the efficiency of the initial cyclization to the spirocyclic vinylidene species. Due to it's conformational restrictions the cyclohexyl substituent does not place C,H bonds close to the vinylidene carbon.



Scheme 7. Synthesis of spirocyclic compound **3x**.

Based on prior mechanistic studies conducted for dual gold-catalyzed reactions.[1] we propose[8] a catalytic scenario as displayed in Scheme 8. The reaction is initiated by the transfer of the two gold fragments from the dual activation catalyst under loss of propyne. The σ,π-activated starting material then undergoes a 5-*endo*-*dig* cyclization forming vinylidene **III**, which then is attacked by the in-plain phenyl group. After formation of the *gem*-diaurated species **V** a transfer of the two gold atoms onto the next starting material under liberation of the product closes the catalytic cycle.[9]

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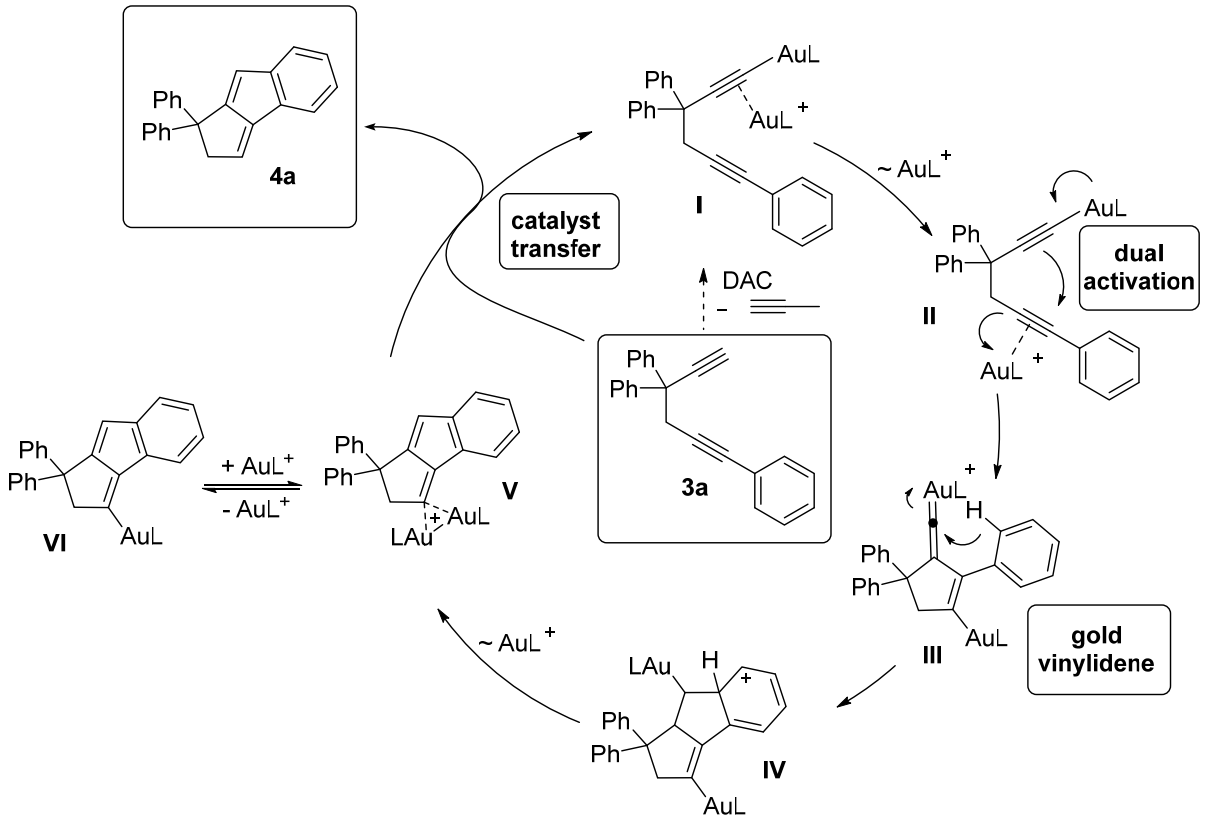

Scheme 8. Catalytic cycle for the formation of **4a**.

In the formation of **4a** the step from intermediate **III** to intermediate **IV** is selectivity-determining. This *positional selectivity* is shown in Scheme 9. The insertion into one of the four symmetry equivalent C-H_a bonds would lead to intermediate **IVa-int** via transition state **IIIa-TS**. On the other hand, an insertion into one of the two symmetry equivalent C-H_b bonds will provide intermediate **VI-int** via **IIIb-TS**. The difference is that the arene bearing H_a is connected to the gold vinylidene by an sp^3-carbon, while H_b is connected by an sp^2-carbon. A computational study revealed that **IIIa-TS** is 3.5 kcal/mol higher than **IIIb-TS**, which perfectly explains the experimentally observed selectivity. Furthermore, intermediate **IVa-int** is 9.8 kcal/mol above **IV-int**., which is in perfect accord with the more extended π-system for the delocalization of the positive charge in **IV-int**. Ultimately, **IV-int** provides **4a** while **IVa-int** leads to **5**, the overall reaction free energies for both pathways (-53.3 kcal/mol, -53.0 kcal/mol) are comparable within the error of the computational study (Scheme 10).

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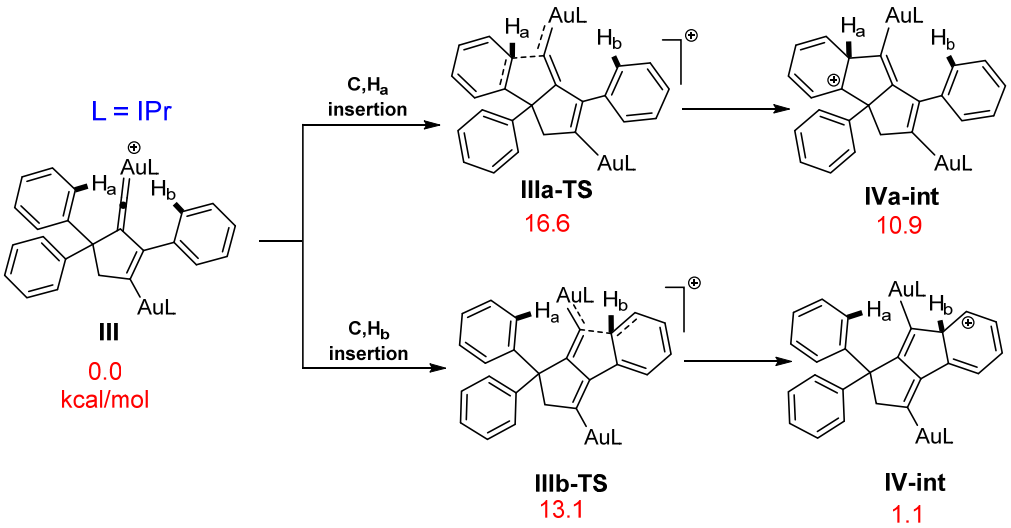
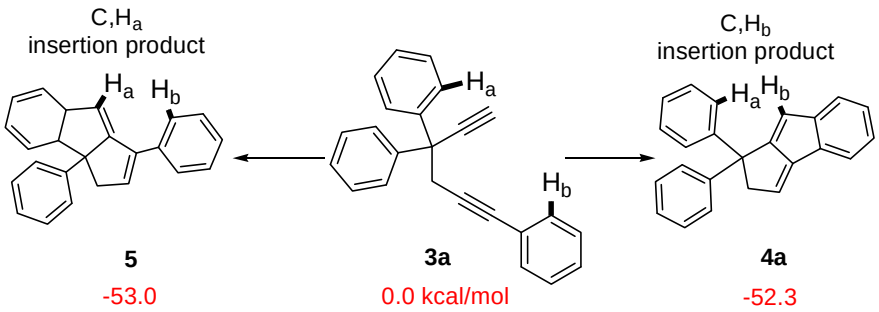


Scheme 9. Computational study of the selectivity-determining step in the anellation leading to **IV-int**.



Scheme 10. Overall reaction free energy of the two competing pathways.

In order to explain the observed *regioselectivity* of the bidirectional synthesis, leading to **4v** but not to the isomer **4v'**, we conducted a computational study focusing on the selectivity-determining step after the first cyclization on one side is already finished and the second cyclization on the other side in the C-C bond-forming step following the formation of intermediate **Int0_L** has two possibilities (Scheme 9).

This computational study clearly revealed that the transition state **TS1_L** and the subsequent intermediate **Int1_L** ultimately leading to the not-observed **4v'** are significantly higher in energy than the corresponding **TS2_L** and the intermediate **Int2_L**, the later indeed leading to the observed product **4v**.

Analyzing the geometry of the two structures of **TS1_L** and **TS2_L** (Figure 3), it becomes obvious that the additional 7.6 kcal/mol in **TS1_L** mainly are caused by a repulsive interaction of the gold complex with one of the phenyl rings on the other end of the molecule, on the end which has formed the benzofulvene substructure in the

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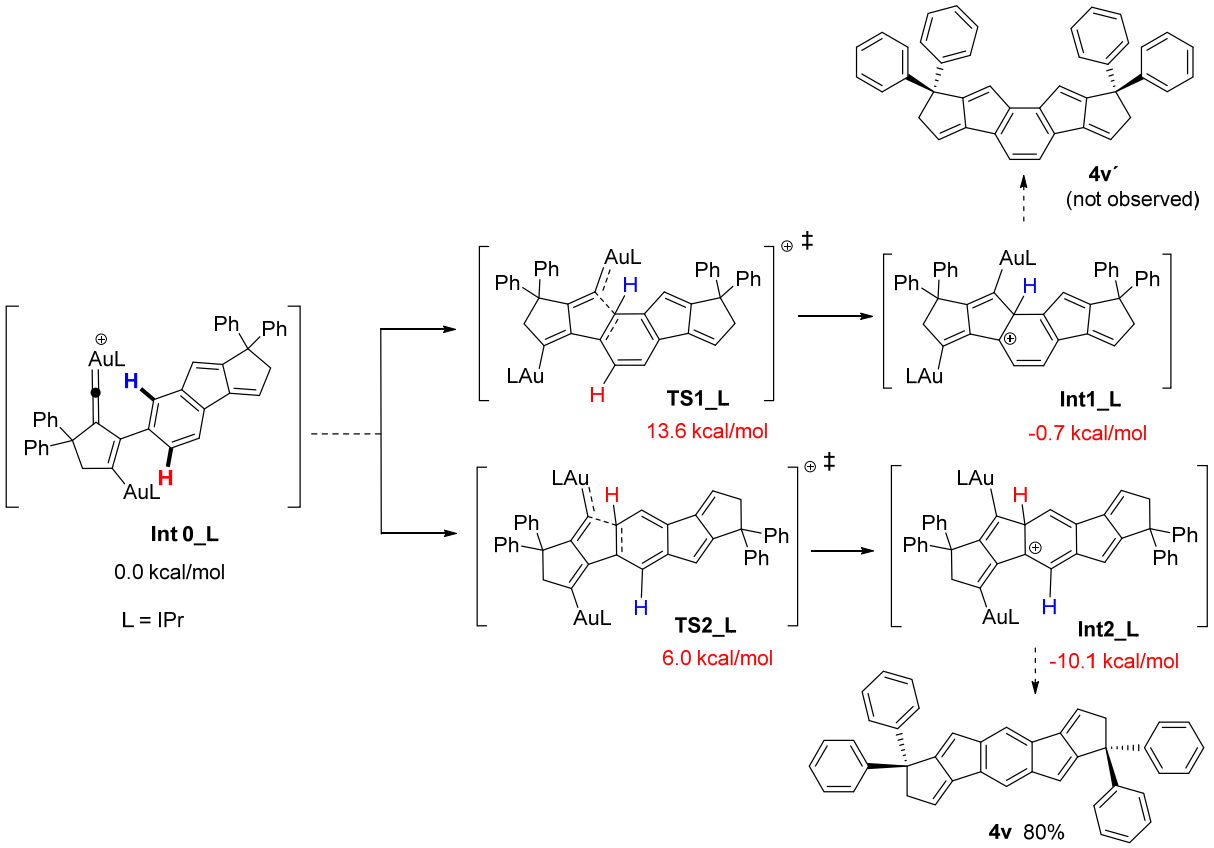
first cylization (in Scheme 11 on the right top side of the molecules, in Figure 3 the steric interaction in the left structure).



Scheme 11. Computational study of the selectivity-determining step in the anellation leading to **4v**.

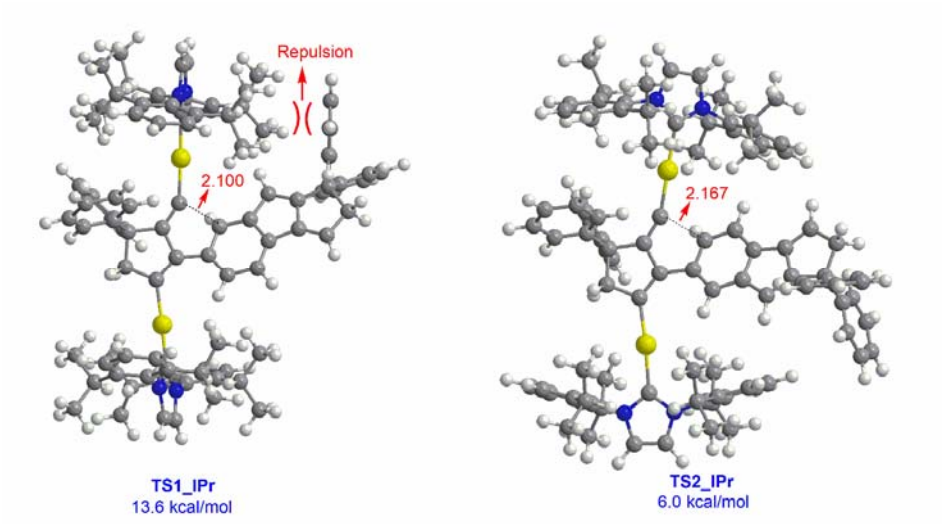


Figure 3. Comparison of the geometries of **TS1_L** and **TS2_L**.

Conclusion

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A novel synthetic approach to previously inaccessible benzofulvene derivates through a selective dual gold-catalyzed 1,5-diyne cyclization was achieved. A remarkable chemoselectivity concerning the C-H activation step leads to the formation of the products in high yields without the formation of byproducts derived from competing CH-insertions. The cyclization occurs under mild reaction conditions, tolerates a broad range of aromatic substituents and even quantitative yields can be obtained by uncomplicated purification methods. By following this methodology complex aromatic systems can be synthesized in an overall short synthetic sequence. In the future this will be an ideal starting point for new extended π-systems for material science.

10.1002/chem.201801031

References

[1] a) L. Ye, Y. Wang, D. H. Aue, L. Zhang, *J. Am. Chem. Soc.* **2012**, *134*, 31 – 34; b) A. S. K. Hashmi, I. Braun, M. Rudolph, F. Rominger, *Organometallics* **2012**, *31*, 644 – 661; c) A. S. K. Hashmi, M. Wieteck, I. Braun, P. Nösel, L. Jongbloed, M. Rudolph, F. Rominger, *Adv. Synth. Catal.* **2012**, *354*, 555 – 562; d) A. S. K. Hashmi, I. Braun, P. Nösel, J. Schädlich, M. Wieteck, M. Rudolph, F. Rominger, *Angew. Chem. Int. Ed.* **2012**, *51*, 4456 – 4460; e) A. S. K. Hashmi, M.Wieteck, I. Braun, M. Rudolph, F. Rominger, *Angew. Chem. Int. Ed.* **2012**, *51*, 10633 – 10637; f) A. Gómez-Suárez, S. P. Nolan, *Angew. Chem. Int. Ed.* **2012**, *51*, 8156 – 8159; g) M. M. Hansmann, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2013**, *52*, 2593 – 2598; h) Y. Wang, A. Yepremyan, S. Ghorai, R. Todd, D. H. Aue, L. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 7795 – 7799; i) D. D. Vachhani, M. Galli, J. Jacobs, L. Van Meervelt, E. V. Van der Eycken, *Chem. Commun.* **2013**, *49*, 7171 – 7173; j) P. Nösel, T. Lauterbach, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2013**, *19*, 8634 – 8641; k) A. S. K. Hashmi, T. Lauterbach, P. Nösel, M. H. Vilhelmsen, M. Rudolph, F. Rominger, *Chem. Eur. J.* **2013**, *19*, 1058 – 1065; l) M. Wieteck, Y. Tokimizu, M. Rudolph, F. Rominger, H. Ohno, N. Fujii, A. S. K. Hashmi, *Chem. Eur. J.* **2014**, *20*, 16331 – 16336; m) M. H. Vilhelmsen, A. S. K. Hashmi, *Chem. Eur. J.* **2014**, *20*, 1901 – 1908; n) M. M. Hansmann, S. Tšupova, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2014**, *20*, 2215 – 2223; o) C. Yu, B. Chen, T. Zhou, Q. Tian, G. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 10903 – 10907; p) Y. Tokimizu, M. Wieteck, M. Rudolph, S. Oishi, N. Fujii, A. S. K. Hashmi, H. Ohno, *Org. Lett.* **2015**, *17*, 604 – 607; q) M. H. Larsen, K. N. Houk, A. S. K. Hashmi, *J. Am. Chem. Soc.* **2015**, *137*, 10668 – 10676; r) J. Bucher, T. Stößer, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed*. **2015**, *54*, 1666 – 1670; s) J. Bucher, T. Wurm, S. Taschinski, E. Sachs, D. Ascough, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Adv. Synth. Catal.* **2017**, *359*, 225 – 233.

[2] a) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem. Int. Ed.* **2006**, *45*, 7896 – 7936; b) A. Füstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410 – 3449; c) N. Bongers, N. Krause, *Angew. Chem. Int. Ed.* **2008**, *47*, 2178 – 2181; d) H. Ohno, *Isr. J. Chem.* **2013**, *53*, 869 – 882; e) D. Pflästerer, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 1331 – 1367.

[3] R. J. Harris, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2015**, *54,* 6867 – 6869.

[4] B. M. Trost, *Science* **1991**, *254*, 5037, 1471 – 1477.

10.1002/chem.201801031

[5] a) R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc., Transactions* **1915**, *107*, 1080 – 1106; b) M. E. Jung, G. Piizzi, *Chem. Rev.* **2005**, *105*, 1735 – 1766.

[6] CCDC 1826439 (**4a**) and 1826440 (**4v**) 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.

[7] G. Chen, Z. Wang, J. Wu, K. Ding, *Org. Lett.* **2008**, *10*, 4573 – 4576.

[8] A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2010**, *49*, 5232 – 5241.

[9] M. H. Larsen, K. N. Houk, A. S. K. Hashmi, *J. Am. Chem. Soc.* **2015**, *137*, 10668 – 10676.

10.1002/chem.201801031

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