How to cite: *Angew. Chem. Int. Ed.* **2020**, *59*, 8522–8526
International Edition: doi.org/10.1002/anie.201914284
German Edition: doi.org/10.1002/ange.201914284

Gold Catalysis

Gold(I)-Catalyzed Cycloisomerization of 3-Alkoxyl-1,6-diynes: A Facile Access to Bicyclo[2.2.1]hept-5-en-2-ones

*Chao Hu, Tao Wang, Matthias Rudolph, Thomas Oeser, Abdullah M. Asiri, and A. Stephen K. Hashmi**

Abstract: *A novel gold-catalyzed cycloisomerization of 1,6-diynes was achieved, providing an atom-economic approach to a diverse set of bicyclo[2.2.1]hept-5-en-2-ones in moderate to good yields. With unsymmetrical starting materials with two different internal alkynyl substituents, to some extent, the regioselectivity could be controlled by both electronic and steric factors. This unprecedented reactivity pattern may inspire new and unconventional strategies for the preparation of bridged ring systems.*

The bicyclo[2.2.1]heptane skeleton is found in a wide range of natural products and pharmaceuticals such as camphor,[1a] sordarin,[1b] SPK 601,[1c] and AMG 221[1d] (Figure 1). Consequently, considerable efforts have been devoted to the development of effective approaches for their synthesis.[2] One of the most commonly employed strategies relies on [4+2] Diels–Alder cycloadditions with their particular efficiency.[2,3] However, high regioselectivity remains problematic in complex unsymmetrical reagents. Efficient and rapid routes for the assembly of bicyclo[2.2.1]heptanes will be beneficial for synthesis.

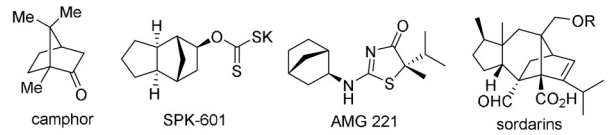
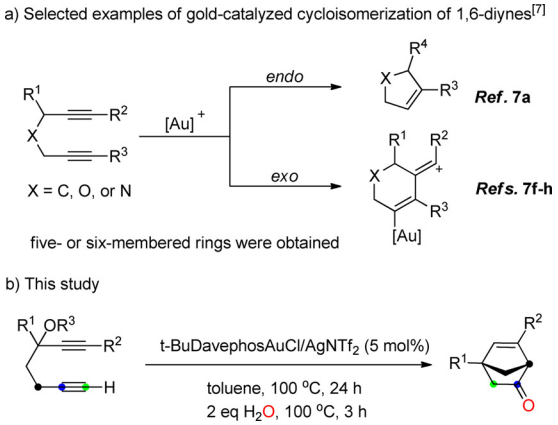


Figure 1. Selected compounds containing a [2.2.1] bicyclic skeleton.

Gold-catalyzed cascade transformations have become a powerful tool for the rapid assembly of complex molecules in a step- and atom-economical route.[4] In 2000, Hashmi and co-workers reported pioneering work on cycloisomerization of 1,6-diynes, affording a furan-anellated spirocycle in 61% yield in the presence of a simple $AuCl_3$ catalyst.[5] Subsequently, many reports on gold-catalyzed cycloisomerization of 1,6-diynes contributed to strategies critical for the preparation of functionalized carbocyclic and heterocyclic compounds.[6] Depending on the structure of the diyne precursors and whether cyclization occurs in an *exo*- or *endo*-fashion, various five- or six-membered cyclic architectures including pyrrolidine,[7a] pyrones,[7b] cyclopenta[b]indoles,[7c] benzo[b]fluorenes,[7d] and naphthalenes[7e] have efficiently been assembled (Scheme 1a). Despite these significant advances,



Scheme 1. Previous studies and our design.

successful examples involving gold-catalyzed 1,6-diyne cycloisomerization in the synthesis of the bridged ring systems are limited to only a few cases which required complicated starting materials.[8] For example, Gagné and co-workers reported an efficient and highly diastereoselective method to the 1,2-trimethylenenorbornane core from designed ACP-containing 1,6-diyne. However, only ten successful examples were reported.[8a] Fiksdahl and co-workers discovered an useful access to bicyclic lactones by combining an initial lactone formation and a second enyne cyclization, but the selectivity remained a challenge and the best yield was 59%.[8b]

Gold-catalyzed intramolecular alkoxylation-initiated skeletal-rearrangement reactions have become well-established during the last decade.[9] Various transformations, such

[*] M. Sc. C. Hu, M. Sc. T. Wang, Dr. M. Rudolph, Dr. T. Oeser, Prof. Dr. A. S. K. Hashmi
Organisch-Chemisches Institut, Heidelberg University
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
E-mail: hashmi@hashmi.de
Homepage: http://www.hashmi.de
A. M. Asiri, Prof. Dr. A. S. K. Hashmi
Chemistry Department, Faculty of Science, King Abdulaziz University
Jeddah 21589 (Saudi Arabia)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201914284.

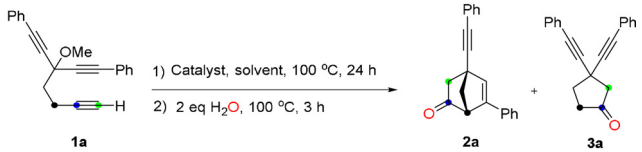
as alkoxylation/Claisen rearrangement,[9a,b] Petasis–Ferrier rearrangement,[9c] and alkoxylation/aza-Prins reaction[9d] were achieved by utilizing this strategy as elegantly established by Toste's, Rhee's or Hashmi's group. Based on these reports and our interest in diyne chemistry,[10] we envisioned that a new mode of gold-catalyzed cycloisomerization of 1,6-diynes would be possible when using a corresponding alkoxylation as the initiated step. Herein, we describe an efficient method for the formation of synthetically useful substituted bicyclo[2.2.1]hept-5-en-2-ones in moderate to good yields and moderate regioselectivity. The conversion is based on a gold-catalyzed cycloisomerization of simple 3-alkoxyl-1,6-diynes in a sequential carboalkoxylation/skeletal-rearrangement/enyne cyclization/hydrolysis cascade (Scheme 1b). Notably, unlike previous reports on gold-catalyzed transformations of diynes,[10c] this unprecedented reactivity pattern nicely complements known conversions of such substrates.

First, we tested **1a** under different conditions (Table 1). **1a** with 5 mol% CyJohnPhosAuCl/$AgNTf_2$ at 100 °C, DCE, 24 h, subsequently 2 equivalents H_2O, 100 °C, 3 h, afforded the desired product **2a** (8%) and 78% of the side product **3a** (entry 1). The latter is consistent with previous reports.[9] Subsequently, a series of solvents with low polarity, such as PhCl, toluene or benzene, were examined. A high selectivity for **2a** was observed with all of them, toluene being best (entries 2–4). Using $C_6H_5NO_2$ as solvent, the substrate was almost entirely transformed to **3a** (entry 5). Among a series of phosphane and carbene ligands in toluene (entries 3 and 6–11), the gold catalyst with t-BuDavePhos as ligand showed high catalytic reactivity and raised the yield to 71% (entry 9). Simple salts like AuCN, AuCl, and $KAuBr_4$ exhibited no catalytic activity (entry 12). A brief screening of counter anions[11] revealed that SbF_6^- and BF_4^- were much worse than NTf_2^- with regard to the reaction yield (entries 13,14). No further improvement was observed when screening at different temperatures (entries 15,16). The control experiments showed no catalytic activity with coordinatively saturated gold complexes or silver salts alone (entries 17,18).

With the optimal reaction conditions in hand, we turned our attention to the scope of this transformation (Table 2). Substrates bearing an electron-donating Me group (**2b**, **2g**, **2h**) usually gave the corresponding products in slightly higher yields than substrates with the electron-withdrawing groups F and Cl (**2d**, **2e**). However, the stronger electron-donating MeO- gave a lower yield of **2c** and a mixture of unidentified products. For the presence of a substituent at different positions, *meta*-position showed slightly higher reactivity in terms of yields (**2b**, **2g**, and **2h**). The dimethyl-substituted substrates **1i** and **1j** were viable for producing the corresponding products **2i** and **2j** in moderate yield. Naphenlene **1k** and the hetero-aromatic **1l** could also be converted. Both linear and branched aliphatic starting materials decomposed (**2m** and **2n**).

Further studies concerning the regioselectivity were carried out with unsymmetrical substrates (Table 3). Under

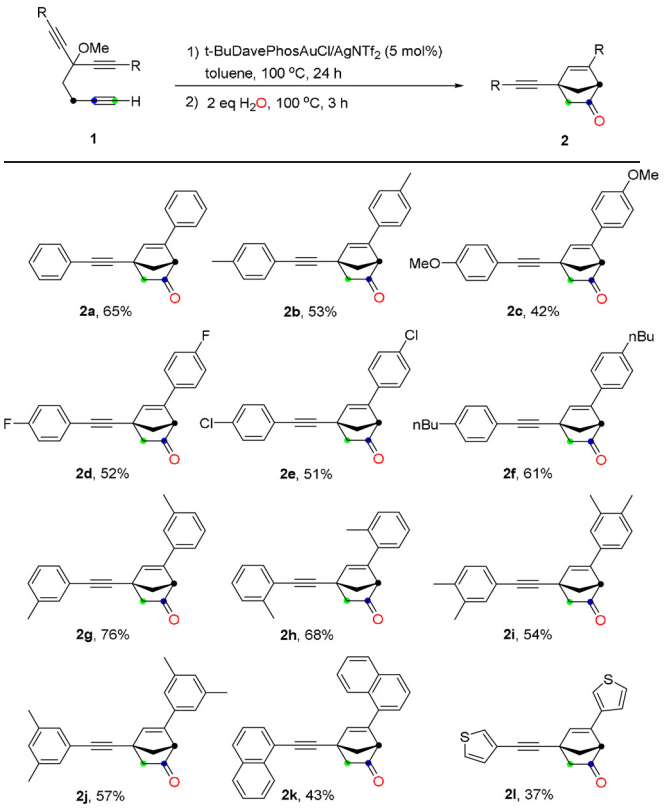
Table 1: Screening for the optimal reaction conditions.[a]



Entry	Catalyst	solvent	Yield[b] [%] 2a	3a
1	CyJohnPhosAuCl/$AgNTf_2$	DCE	8	78
2	CyJohnPhosAuCl/$AgNTf_2$	PhCl	43	5
3	CyJohnPhosAuCl/$AgNTf_2$	toluene	49	8
4	CyJohnPhosAuCl/$AgNTf_2$	bezene	25	<5
5	CyJohnPhosAuCl/$AgNTf_2$	$C_6H_5NO_2$	0	97
6	JohnPhosAuCl/$AgNTf_2$	toluene	38	<5
7	IPrAuCl/$AgNTf_2$	toluene	53	13
8	$Ph_3PAuCl/AgNTf_2$	toluene	43	11
9	**t-BuDavePhosAuCl/$AgNTf_2$**	**toluene**	**71**	**8**
10	t-BuMePhosAuCl/$AgNTf_2$	toluene	49	16
11	t-BuXPhosAuCl/$AgNTf_2$	toluene	44	15
12	AuCN or AuCl or $KAuBr_4$	toluene	0	0
13	t-BuDavePhosAuCl/$AgSbF_6$	toluene	46	<5
14	t-BuDavePhosAuCl/$AgBF_4$	toluene	37	<5
15[c]	t-BuDavePhosAuCl/$AgNTf_2$	toluene	62	11
16[d]	t-BuDavePhosAuCl/$AgNTf_2$	toluene	65	12
17	t-BuDavePhosAuCl	toluene	0	0
18	$AgNTf_2$	toluene	0	0

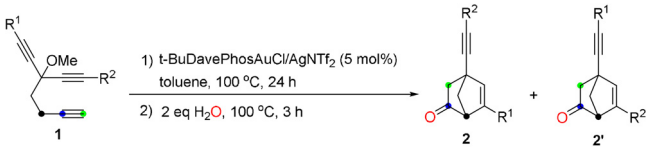
[a] All reactions were carried out with **1** (0.1 mmol), 5 mol% catalyst toluene (1 mL) at 100 °C for 24 h, 2 equivalents H_2O for another 3 h under same condition. [b] Determined by ^1H NMR with 1,3,5-trimethoxybenzene as the internal standard. [c] at 90 °C. [d] at 110 °C.

Table 2: Scope of the reaction for symmetric starting materials.[a,b]



[a] standard conditions: **1a** (0.1 mmol), 5 mol% catalyst, toluene (1 mL) at 100 °C for 24 h, 2 equivalents H_2O for another 3 h under same condition. [b] Yields of isolated products. [c] Decomposed substrates R = propyl (**1m**), R = t-Bu (**1n**).

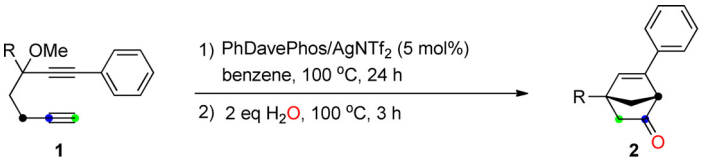
Table 3: Scope of the reaction for unsymmetrical starting materials.[a,b]



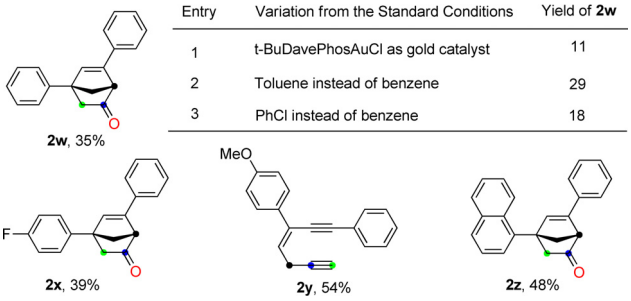
Entry	R^1	R^2	Yield[b] [%] 2	2′
1	Ph (**1o**)	4-FC_6H_5	**2o**, 24	**2o′**, 36
2	Ph (**1p**)	4-ClC_6H_5	**2p**, 23	**2p′**, 43
3	Ph (**1q**)	3,5diMeC_6H_5	**2q**, 34	**2q′**, 27
4	Ph (**1r**)	4-$CF_3C_6H_5$	**2r**, 0	**2r′**, 48
5	Ph (**1s**)		**2s**, 0	**2s′**, 42
6	Ph (**1t**)		**2t**, 11	**2t′**, 44
7	Ph (**1u**)	t-Bu	**2u**, 43	**2u′**, 7
8	Ph (**1v**)		**2v**, 35	**2v′**, 27

[a] standard conditions: **1a** (0.1 mmol), 5 mol% catalyst, toluene (1 mL) at 100 °C for 24 h, 2 equivalents H_2O for another 3 h under same condition. [b] Yields of isolated products.

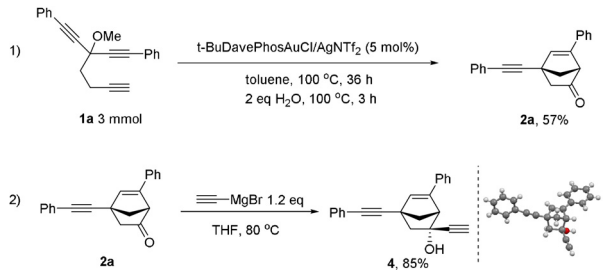
Table 4: Reaction scope with non-alkynyl substituent.[a,b,c]



Entry	Variation from the Standard Conditions	Yield of **2w**
1	t-BuDavePhosAuCl as gold catalyst	11
2	Toluene instead of benzene	29
3	PhCl instead of benzene	18



[a] standard conditions: **1a** (0.2 mmol), 5 mol% catalyst, benzene (1 mL) at 100 °C for 24 h, 2 equivalents H_2O for another 3 h under same condition. [b] Yields of isolated products. [c] Decomposed substrate R = ethyl (**1aa**).



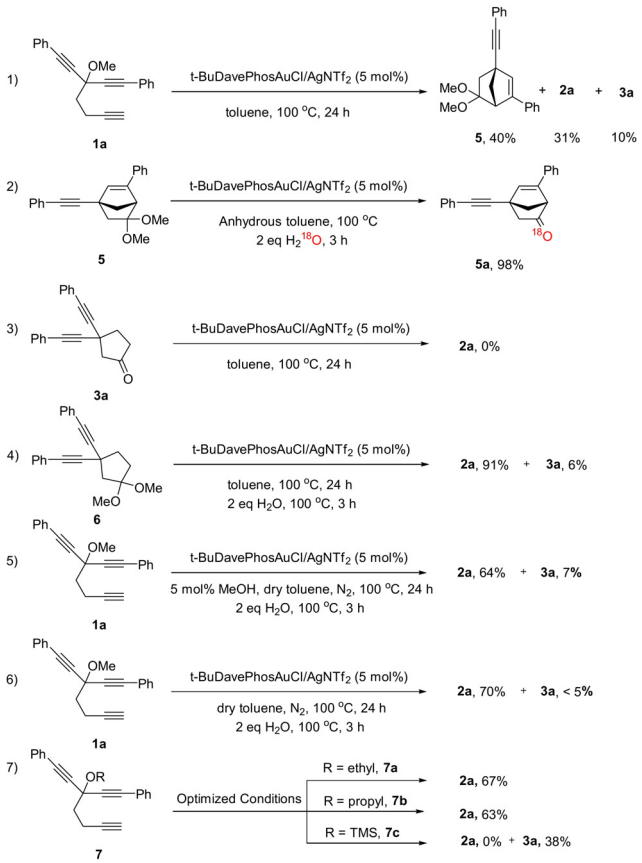
Scheme 2. Gram-scale synthesis and subsequent conversion.

the optimized conditions, substrates **1o**, **1p** and **1q** could smoothly be transferred to the corresponding product, however, with poor regioselectivities (entries 1–3). A significantly higher selectivity was observed when $CF_3C_6H_5$ with a stronger electron-withdrawing group was used as R^2 (entry 4). These observations revealed that the regioselectivity could be controlled by electronic effects, especially when there is a strong electronic difference between R^1 and R^2. Substrate **1s**, containing a naphthalene, was tested and afforded **2s′** as the only product (entry 5). Substrate **1t** (entry 6) with a combination of a phenyl and a thiophenyl group also showed higher regioselectivity, providing **2t** and **2t′** in a 1:4 ratio. Subsequently, we tested the effect of steric hindrance, compared to the less bulky group cyclohexyl, substrate with a more sterically hindered *t*Bu moiety (**1u**) exhibited a higher regioselectivity (entries 7,8).

An extension of the substrate's scope with non-alkynyl substituents is shown in Table 4. Substrates with electron-deficient or bulky aryl groups were compatible under the adjusted conditions (**2x**, **2z**) while for **1y** bearing an electron-donating substituent only the elimination product was obtained, which can be attributed to the stabilization of the intermediate cation. The ethyl-tethered substrate **1aa** decomposed.

An upscaling of the reaction is also possible, 3 mmol of **1a** were subjected to the optimized condition, **2a** was obtained with 57% isolated yield [Scheme 2, Eq. (1)]). Moreover, treatment of **2a** with 1.2 equivalent ethynylmagnesium bromide gave exclusively the *exo*-addition product 4 [85% yield, Scheme 2, Eq. (2)].[12] The structural assignment of compound **4** was further confirmed by single-crystal X-ray structure analysis.[13]

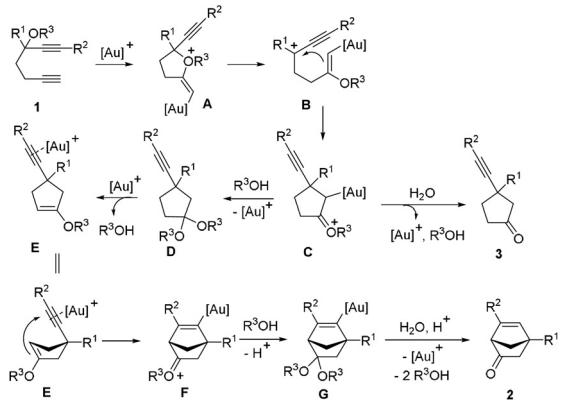
Preliminary mechanistic studies are shown in Scheme 3. Treatment of the substrate **1a** with the gold catalyst for 24 h led to a mixture of ketal **5** (40%), **2a** (31%) and **3a** (10%). The ketal **5** could completely be converted to the corresponding product **2a** (98%) through hydrolysis, which was confirmed by an ^{18}O-labelling experiment. This result clearly demonstrated the possibility of hydrolysis as the final step [Scheme 3, Eq. (1) and (2)]. Next, on the base of previous reports on gold-catalyzed Conia-Ene reaction,[14] we wondered if **3a** might be an intermediate of the catalytic cycle. However, no conversion to product **2a** was detected when **3a** was subjected to the standard reaction conditions [Scheme 3, Eq. (3)]. We then turned our attention on the reactivity of ketal **6**,[15] which under these reaction conditions turned out to be a productive intermediate in the catalytic cycle, and this could be demonstrated by its further conversion to product **2a** under the optimal conditions in excellent yield [Scheme 3, Eq. (4)]. A small amount of MeOH, which can originate from β-elimination of the substrate (see Table 4, **2y**), seems to be sufficient to close the first catalytic cycle [Scheme 3, Eq. (6)]. A higher concentration of MeOH leads to lower yields [Eq. (5)], probably due to a competing nucleophilic addition to the alkyne.[15b] A brief screening of the OR group is depicted in Eq. (7), both ethyl and propyl were compatible



Scheme 3. Mechanistic investigation.

under the optimized conditions. **7c** bearing a TMS substituent delivered only hydrolysis product **3a**.

Based on these observations and analogies to previous reports,[15b,16] the proposed catalytic mechanism is depicted in Scheme 4. Initially, in the presence of a gold catalyst, the vinyl gold intermediate **A** is formed through gold-catalyzed alkoxycyclization, followed by a C–O bond cleavage and a cyclization to intermediate **C. C** could directly be transferred to product **3** through hydrolysis or be attacked by the R^3OH generated in situ (from hydrolysis or elimination) to form intermediate **D. D** could then undergo a gold-catalyzed β-elimination providing the cyclopentene intermediate **E**,



Scheme 4. Possible reaction mechanisms.

which subsequently undergoes a sequence of enyne cyclization, nucleophilic addition, and hydrolysis reactions to the final product **2**.

In conclusion, we have developed an unprecedented gold-catalyzed 1,6-diyne cycloisomerization by using carboalkoxylation as the initiated step. The new reaction provides very interesting access to bridged ring systems (bicyclo-[2.2.1]heptane derivatives), while many other reactions of 1,6-diynes are restricted to the synthesis of monocyclic or anellated five- or six-membered rings. This represents remarkable progress with respect to the product scope. Studies are currently underway in our laboratory to apply this strategy to the synthesis of other bridged ring systems.

Acknowledgements

C.H. and T.W. are grateful to the CSC (China Scholarship Council) for a PhD fellowship.

Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,6-diynes · bicyclo[2.2.1]heptane · bridged ring · gold catalysis

[1] a) K. C. Nicolaou, T. Montagnon, *Molecules That Changed The World*, Wiley-VCH, Weinheim, **2008**, p. 29; b) H. Liang, *Beilstein J. Org. Chem.* **2008**, *4*, 31; c) R. M. Adibhatla, J. F. Hatcher, A. Gusain, *Neurochem. Res.* **2012**, *37*, 671; d) A. Li, C. C. Yuan, D. Chow, M. Chen, M. G. Emery, C. Hale, X. Zhang, R. Subramanian, D. J. St. Jean, R. Komorowski, M. Véniant, M. Wang, C. Fotsch, *ACS Med. Chem. Lett.* **2011**, *2*, 824; e) Y. Matsuo, H. Sakagami, Y. Mimaki, *Chem. Pharm. Bull.* **2014**, *62*, 1192; f) T. Satou, Y. Ogawa, K. Koike, *Phytother. Res.* **2015**, *29*, 1246; g) M. Blümel, S. Nagasawa, K. Blackford, S. R. Hare, D. J. Tantillo, R. Sarpong, *J. Am. Chem. Soc.* **2018**, *140*, 9291.

[2] a) J.-G. Fu, Y.-F. Shan, W.-B. Sun, G.-Q. Lin, B.-F. Sun, *Org. Biomol. Chem.* **2016**, *14*, 5229; b) M. Narisada, M. Ohtani, F. Watanabe, K. Uchida, H. Arita, M. Doteuchi, K. Hanasaki, H. Kakushi, K. Otani, S. Hara, *J. Med. Chem.* **1988**, *31*, 1847; c) D. Liang, Y. Zou, Q. Wang, A. Goeke, *J. Org. Chem.* **2014**, *79*, 6726; d) A. K. Ghosh, K. V. Rao, P. R. Nyalapatla, H. L. Osswald, C. D. Martyr, M. Aoki, H. Hayashi, J. Agniswamy, Y.-F. Wang, H. Bulut, D. Das, I. T. Weber, H. Mitsuya, *J. Med. Chem.* **2017**, *60*, 4267; e) E. Plettner, A. Mohle, M. T. Mwangi, J. Griscti, B. O. Patrick, R. Nair, R. J. Batchelor, F. Einstein, *Tetrahedron: Asymmetry* **2005**, *16*, 2754.

[3] a) R. Mose, M. E. Jensen, G. Preegel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, *54*, 13630; *Angew. Chem.* **2015**, *127*, 13834; b) M. Tsakos, M. R. J. Elsegood, C. G. Kokotos, *Chem. Commun.* **2013**, *49*, 2219; c) X. Feng, Z. Zhou, R. Zhou, Q. Q. Zhou, L. Dong, Y. C. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 19942; d) M. Rueping, A. Kuenkel, R. Fröhlich, *Chem. Eur. J.* **2010**, *16*, 4173; e) B. Tan, Y. Lu, X. Zeng, P. J. Chua, G. Zhong, *Org. Lett.* **2010**, *12*, 2682; f) H. Sundén, R. Rios, Y. M. Xu, L. Eriksson, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 2549.

[4] a) J. L. Mascareñas, I. Varela, F. López, *Acc. Chem. Res.* **2019**, *52*, 465; b) Y. Y. Li, W. B. Li, J. L. Zhang, *Chem. Eur. J.* **2017**, *23*, 467;

c) J. Xie, C. Pan, A. Abdukader, C. Zhu, *Chem. Soc. Rev.* **2014**, *43*, 5245; d) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem. Int. Ed.* **2006**, *45*, 7896; *Angew. Chem.* **2006**, *118*, 8064; e) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395; f) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208; g) A. S. K. Hashmi, *Acc. Chem. Res.* **2014**, *47*, 864.

[5] A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; *Angew. Chem.* **2000**, *112*, 2382.

[6] a) A. S. K. Hashmi, M. Rudolph, H.-U. Siehl, M. Tanaka, J. W. Bats, W. Frey, *Chem. Eur. J.* **2008**, *14*, 3703; b) N. Asao, K. Sato, *Org. Lett.* **2006**, *8*, 5361; c) J. Yan, G. L. Tay, C. Neo, B. R. Lee, P. W. H. Chan, *Org. Lett.* **2015**, *17*, 4176; d) A. S. K. Hashmi, M. Hamzic, M. Rudolph, M. Ackermann, F. Rominger, *Adv. Synth. Catal.* **2009**, *351*, 2469; e) D. Lebœuf, A. Simonneau, C. Aubert, M. Malacria, V. Gandon, L. Fensterbank, *Angew. Chem. Int. Ed.* **2011**, *50*, 6868; *Angew. Chem.* **2011**, *123*, 7000; f) C. H. Oh, J. H. Kim, L. Piao, J. Yu, S. Y. Kim, *Chem. Eur. J.* **2013**, *19*, 10501; g) K. Ji, X. Liu, B. Du, F. Yang, J. Gao, *Chem. Commun.* **2015**, *51*, 10318; h) X. Tian, L. Song, K. Farshadfar, M. Rudolph, F. Rominger, T. Oeser, A. Ariafard, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2020**, *59*, 471; *Angew. Chem.* **2020**, *132*, 479.

[7] a) D.-H. Zhang, L.-F. Yao, Y. Wei, M. Shi, *Angew. Chem. Int. Ed.* **2011**, *50*, 2583; *Angew. Chem.* **2011**, *123*, 2631; b) T. Luo, M. Dai, S. Zheng, S. L. Schreiber, *Org. Lett.* **2011**, *13*, 112834; c) J. Liu, M. Chen, L. Zhang, Y. Liu, *Chem. Eur. J.* **2015**, *21*, 1009; d) Y. Chen, M. Chen, Y. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 6493; *Angew. Chem.* **2012**, *124*, 6599; e) C. H. Oh, J. H. Kim, B. K. Oh, J. R. Park, J. H. Lee, *Chem. Eur. J.* **2013**, *19*, 2592; f) J.-J. Lian, P.-C. Chen, Y.-P. Lin, H.-C. Ting, R.-S. Liu, *J. Am. Chem. Soc.* **2006**, *128*, 11372; g) T. Shibata, R. Fujiwara, D. Takano, *Synlett* **2005**, 2062; h) D. D. Vachhani, M. Galli, J. Jacobs, L. Van Meervelt, E. V. van der Eycken, *Chem. Commun.* **2013**, *49*, 7171.

[8] a) H. Zheng, L. L. Adduci, R. J. Felix, M. R. Gagné, *Angew. Chem. Int. Ed.* **2014**, *53*, 7904; *Angew. Chem.* **2014**, *126*, 8038; b) C. A. Sperger, A. Fiksdahl, *J. Org. Chem.* **2010**, *75*, 4542; c) J. Meng, Y. Zhao, C. Ren, Y. Li, Z. Li, Q. Liu, *Chem. Eur. J.* **2009**, *15*, 1830.

[9] a) H. Wu, W. Zi, G. Li, H. Lu, F. D. Toste, *Angew. Chem. Int. Ed.* **2015**, *54*, 8529; *Angew. Chem.* **2015**, *127*, 8649; b) H. J. Bae, B. Baskar, S. E. An, J. Y. Cheong, D. T. Thangadurai, I. C. Hwang, Y. H. Rhee, *Angew. Chem. Int. Ed.* **2008**, *47*, 2263 – 2266; *Angew. Chem.* **2008**, *120*, 2295 – 2298; c) H. Kim, Y. H. Rhee, *J. Am. Chem. Soc.* **2012**, *134*, 4011; d) H. J. Bae, W. Jeong, J. H. Lee, Y. H. Rhee, *Chem. Eur. J.* **2011**, *17*, 1433; e) W. Zi, H. Wu, F. D. Toste, *J. Am. Chem. Soc.* **2015**, *137*, 3225; f) M. C. B. Jaimes, V. Weingand, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2013**, *19*, 12504; g) M. Ackermann, J. Bucher, M. Rappold, K. Graf, F. Rominger, A. S. K. Hashmi, *Chem. Asian J.* **2013**, *8*, 1786; h) M. Zhang, Y. Wang, Y. Yang, X. Hu, *Adv. Synth. Catal.* **2012**, *354*, 981; i) P. Davies, H. Adcock, *Synthesis* **2012**, *44*, 3401; j) C. M. Ting, C. D. Wang, R. Chaudhuri, R.-S. Liu, *Org. Lett.* **2011**, *13*, 1702; k) F. M. Istrate, F. Gagosz, *Beilstein J. Org. Chem.* **2011**, *7*, 878; l) M. Uemura, I. D. Watson, M. Katsukawa, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 3464; m) P. Dubé, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 12062.

[10] a) I. Braun, A. M. Asiri, A. S. K. Hashmi, *ACS Catal.* **2013**, *3*, 1902; b) D. Pflästerer, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 1331; c) A. M. Asiri, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 4471; d) X. Zhao, M. Rudolph, A. S. K. Hashmi, *Chem. Commun.* **2019**, *55*, 12127.

[11] a) J. Schießl, M. Rudolph, A. S. K. Hashmi, *Adv. Synth. Catal.* **2017**, *359*, 639; b) J. Schießl, P. M. Stein, J. Stirn, K. Emler, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Adv. Synth. Catal.* **2019**, *361*, 725.

[12] a) A. Köpfer, B. Breit, *Angew. Chem. Int. Ed.* **2015**, *54*, 6913; *Angew. Chem.* **2015**, *127*, 7017; b) G. P. Moss, *Pure Appl. Chem.* **1996**, *68*, 2193.

[13] CCDC 1958788 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[14] a) J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4526; b) S. T. Staben, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem. Int. Ed.* **2004**, *43*, 5350; *Angew. Chem.* **2004**, *116*, 5464.

[15] a) J. Dong, L. Yu, J. Xie, *ACS Omega* **2018**, *3*, 4974; b) C. Sperger, A. Fiksdahl, *Org. Lett.* **2009**, *11*, 2449.

[16] a) O. N. Faza, C. S. Lýpez, A. R. de Lera, *J. Org. Chem.* **2011**, *76*, 3791; b) N. T. Patil, *Chem. Asian J.* **2012**, *7*, 2186.

Manuscript received: November 8, 2019
Revised manuscript received: January 22, 2020
Accepted manuscript online: January 23, 2020
Version of record online: March 24, 2020

