Silver(I)-Catalyzed Intramolecular Cyclizations of Epoxide-Propargylic Esters to 1,4-Oxazine Derivatives

Peng-Hua Li,[a] Jin-Ming Yang,[a] Yin Wei,[b] and Min Shi*[a, b]

An interesting silver(I)-catalyzed, one-pot intramolecular cyclization of epoxide-propargylic esters is described. A variety of 1,4-oxazine derivatives were obtained through a novel domino sequence, including three-membered ring-opening, 3,3-sigmatropic rearrangement, 6-*exo*-cycloisomerization and subsequent intramolecular elimination in moderate yields under mild conditions.

Among the variety of transition-metal-catalyzed transformations of alkynes that have achieved significant development to date,[1] the transformations with regard to oxo-functionalization of alkynes have attracted special interest.[2] Cyclizations of epoxy alkynes have provided rapid access to complex molecular structures in an easy one-pot process, in which a wide range of metal complexes such as those with gold or silver can be used, either in a stoichiometric or a catalytic manner.[3]

Alkynyl epoxides can be divided into two parts: non-tethered alkynyl epoxides and X-tethered alkynyl compounds (X= C, N, O). In general, transition-metal-catalyzed reactions of alkynyl epoxides can start from an alkynyl moiety or an epoxide moiety, and the general reaction modes have been shown in Scheme 1. For instance, Krause and co-workers reported that, when alkynyl epoxide compounds were catalyzed by a copper hydride catalyst, a vinylcopper intermediate can be formed through a *syn* addition of the copper hydride to the triple bond, and vinyl oxirane can be obtained in the presence of an alcohol by a protodemetalation process (Scheme 1a).[3h] On the other hand, in the presence of a gold catalyst, the addition of alkynyl oxiranes (R^1=H, R^2 and R^3=—CH$_2$(CH$_2$)$_3$CH$_2$—) with an oxidizing agent such as pyridine oxide at the terminal position of the alkynyl moiety could produce an allenyl–metal alkoxide in-
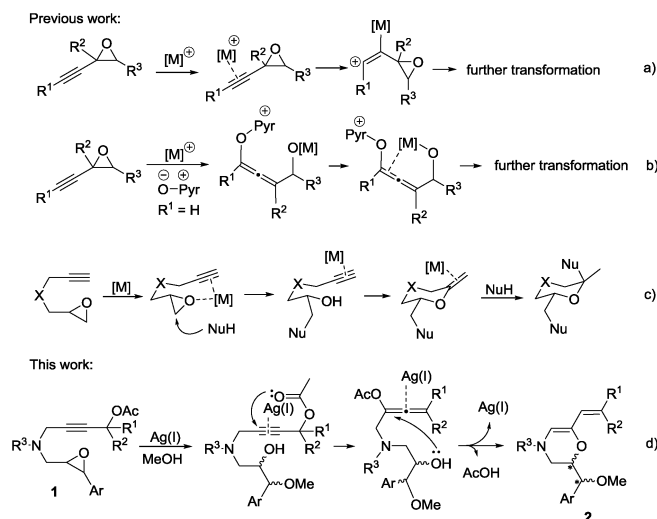
Scheme 1. General reaction modes of alkynyl epoxides in the presence of transition-metal catalysts.

termediate that would play a key role of the nucleophilic addition in the next scenario (Scheme 1b).[4] In this respect, our group has also reported a gold-catalyzed intramolecular cascade cyclization reaction of N-tethered alkynyl epoxides to afford a variety of ketal skeletons derivatives under mild conditions (Scheme 1c).[5]

As a part of our continuous interest in transition-metal-catalyzed or -mediated reactions of alkynyl epoxide and propargylic ester compounds,[5,6] we designed a variety of N-tethered epoxide-propargylic ester compounds and, herein, we report our investigation on silver-catalyzed transformation of these compound to 3,4-dihydro-1,4-oxazine derivatives via a domino process including three-membered ring-opening, 3,3-sigmatropic rearrangement, 6-*exo*-cycloisomerization and subsequent intramolecular elimination (Scheme 1d).
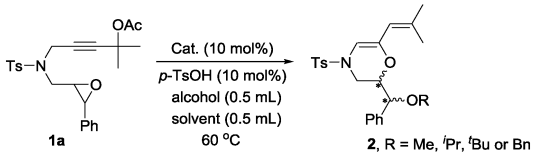
Initially, we commenced our investigation by using epoxide-propargylic ester **1a** as a model substrate to optimize the reaction conditions. The results are summarized in Table 1. We found an interesting six-membered 1,4-oxazine product, **2a**, which was formed in a total yield of 53% along with 1:2 d.r. within 1 h upon treating **1a** with AgSbF$_6$, *p*-toluenesulfonic acid (*p*-TsOH) in anhydrous 1,2-dichloroethane (DCE) and methanol (MeOH) at 60 °C (Table 1, entry 1). However, when **1a** was treated with other metal catalysts, such as Yb(OTf)$_3$, Sc(OTf)$_3$, Ph$_3$PAuCl/Yb(OTf)$_3$, Ph$_3$PAuCl/AgSbF$_6$, or **Au-1**, no desired product was obtained (Table 1, entries 2–6). The reason for the failure of gold(I) catalysts is that, as compared to the corresponding donor-substituted alkynes,[7] gold(I) catalysts might be too reactive and can easily or efficiently coordinate to the electron-
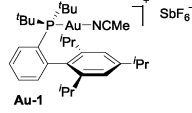
[a] *P.-H. Li, J.-M. Yang, Prof. M. Shi*
Key Laboratory for Advanced Materials and Institute of Fine Chemicals
School of Chemistry and Molecule Engineering
East China University of Science and Technology
130 Mei Long Road, Shanghai 200237 (P. R. China)

[b] *Dr. Y. Wei, Prof. M. Shi*
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
University of Chinese Academy of Sciences, Chinese Academy of Sciences
345 Linglin Lu, Shanghai 200032 (P. R. China)
E-mail: mshi@mail.sioc.ac.cn

Table 1. Optimal reaction conditions for the intramolecular cyclizations.

Entry[a]	Catalyst	Alcohol	Solvent	T [h]	Yield [%][b]	d.r.[c]
1	AgSbF$_6$	MeOH	DCE	1	53	1:2
2	Yb(OTf)$_3$	MeOH	DCE	10	trace	–[g]
3	Sc(OTf)$_3$	MeOH	DCE	10	trace	–[g]
4	Ph$_3$PAuCl/Yb(OTf)$_3$	MeOH	DCE	12	trace	–[g]
5	Ph$_3$PAuCl/AgSbF$_6$	MeOH	DCE	10	trace	–[g]
6	Au-1	MeOH	DCE	10	trace	–[g]
7	AgBF$_4$	MeOH	DCE	1	56	1:1.7
8	AgOTs	MeOH	DCE	1	62	1:2.2
9	AgClO$_4$	MeOH	DCE	1	62	1:1.7
10	AgOTf	MeOH	DCE	1	60	1:2.1
11	CF$_3$CO$_2$Ag	MeOH	DCE	1	37	1:2.2
12	AgNO$_2$	MeOH	DCE	5	42	1:1.8
13	AgNO$_3$	MeOH	DCE	12	trace	–[g]
14	AgOAc	MeOH	DCE	12	trace	–[g]
15	**AgNTf$_2$**	**MeOH**	**DCE**	**1**	**66**	**1:1.9**
16[d]	AgNTf$_2$	MeOH	DCE	1	49	1:2
17[e]	AgNTf$_2$	MeOH	DCE	1	48	1:2.3
18[f]	AgNTf$_2$	MeOH	DCE	1	45	1:2.6
19[h]	AgNTf$_2$	MeOH	DCE	6	32	1:2.1
20	AgNTf$_2$	MeOH	THF	1	45	1:2.3
21	AgNTf$_2$	MeOH	CH$_3$CN	12	trace	–[g]
22	AgNTf$_2$	MeOH	1,4-dioxane	1	57	1:2
23	AgNTf$_2$	MeOH	bromobenzene	1	21	1:2.2
24	AgNTf$_2$	iPrOH	DCE	2	39	1:1
25	AgNTf$_2$	tBuOH	DCE	2	43	1.6:1
26	AgNTf$_2$	BnOH	DCE	2	37	1:1.9
27	AgNTf$_2$	PhNH$_2$	DCE	12	trace	–[g]
28	AgNTf$_2$	H$_2$O	DCE	12	trace	–[g]

[a] Reaction conditions: 0.1 mmol of **1**; 10 mol% of catalyst; 10 mol% of p-TsOH; 0.5 mL MeOH; 0.5 mL of dry solvent. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy. [d] 0.2 equivalents of p-TsOH were used. [e] 0.3 equivalents of p-TsOH were used. [f] 1.0 equivalents of p-TsOH were used. [g] Not determined. [h] No p-TsOH was used.

rich diene,[8] further enhancing its reactivity and subsequently leading to decomposition of the desired products. Then, various silver(I) catalysts were examined. Under the standard conditions, when AgBF$_4$, AgOTs, AgClO$_4$, AgOTf, CF$_3$CO$_2$Ag, and AgNTf$_2$ were used as the catalysts to carry out the reaction, the desired product **2 a** was obtained in 56, 62, 62, 60, 37, and 66% total yields within 1 h, respectively (Table 1, entries 7–11 and 15). Using AgNO$_2$ as the catalyst gave the desired product **2 a** in 42% total yield within 5 h (Table 1, entry 12). However, when AgNO$_3$ and AgOAc were used as the catalysts, the reaction did not give the desired product **2 a** (Table 1, entries 13 and 14). After identifying AgNTf$_2$ as an appropriate catalyst, we optimized other critical reaction parameters, such as the amount of p-TsOH, solvent, and alcohol. First, we found that increasing the amount of p-TsOH did not afford the better results (Table 1, entries 16–18), but in the absence of p-TsOH, the reac-

tion gave **2 a** in a lower yield (32%) after a longer time (6 h) (Table 1, entry 19) than that in the presence of p-TsOH (Table 1, entry 15). Thus, we believe that p-TsOH was beneficial to the ring-opening process.[5, 9] Then, the solvent effects were also examined by using AgNTf$_2$ as the catalyst. In tetrahydrofuran (THF) and 1,4-dioxane, inferior results were obtained; only a 21% total yield of the desired product **2 a** was obtained in bromobenzene, and when using CH$_3$CN as the solvent, no desired product was obtained (Table 1, entries 19–22). Finally, when iPrOH, tBuOH, BnOH was used as the nucleophilic reagent instead of MeOH, the corresponding products **2** were formed in 39, 43, and 37% yields, respectively (Table 1, entries 23–25). Furthermore, when PhNH$_2$ was used instead of MeOH, none of the desired product was obtained (Table 1, entry 27) because the use of PhNH$_2$ might lead to deactivation of the silver catalyst. When H$_2$O was used as the nucleophilic reagent instead of MeOH, the desired product was again not obtained, perhaps owing to its weaker nucleophilicity and the decomposition of the silver catalyst (Table 1, entry 28).

Thus, the use of AgNTf$_2$ (10 mol%) and p-TsOH (10 mol%) in dry DCE and dry MeOH at 60 °C were found to be the most efficient reaction conditions for this transformation and were used as the optimized conditions.

With the optimized reaction conditions in hand, we next turned our attention to investigate the scope and limitation of this reaction by using a variety of epoxide-propargylic esters **1 b**–**1 o**, and the results are summarized in Table 2. As can be seen from Table 2, all of the reactions proceeded smoothly to give the corresponding products **2 b**–**2 f** in 41–53% total yields and 1:1.2–1:2.2 d.r. at the optimized conditions when R^1/R^2 were ethyl, isopropyl, isobutyl, or cycloalkyl groups, suggesting that the steric effect of R^1/R^2 groups did not have a significant impact on this reaction. When the N-tethered group was replaced by 2-methylbenzenesulfonyl (**1 g**), 2,4,6-trimethylbenzenesulfonyl (Mes, **1 h**), 2,4,6-triisopropylbenzenesulfonyl (**1 i**), and phenylmethanesulfonyl (**1 j**), the corresponding products were obtained in 39, 30, 47, and 39% total yields, respectively. Moreover, irrespective of whether Ar was changed to 1-naphthyl (**1 k**), 4-fluorophenyl (**1 l**), 4-chlorophenyl (**1 m**), or 4-bromophenyl (**1 n**), the reactions proceeded smoothly to give the corresponding products **2 k**–**2 n** in 40–63% yields. As for substrate **1 o**, in which R^3 was a 4-bromobenzenesulfonyl (Bs) group and Ar was replaced with a 4-bromophenyl group, the desired product **2 o** was obtained in 50% total yield along with 1:1.8 d.r. The structure of anti-**2 o** has been unequivocally confirmed by using X-ray diffraction. Its ORTEP drawing is shown in Figure 1 and the related crystal data are presented in the Supporting Information.[10]

Based on the previous literature and our own results,[5, 6a, b] we propose a plausible reaction mechanism for this silver(I)-catalyzed transformation in Scheme 2. The cationic silver(I) first activates the alkynyl group upon coordination with the epoxy group, affording intermediate **A**, which is nucleophilically attacked by methanol to give epoxy ring-opening intermediate **B**. Then, intermediate **B** undergoes a 3,3-sigmatropic rearrangement to give carboxyallenyl intermediate **C**,[11] which undergoes a 6-exo-cycloisomerization to give a six-membered
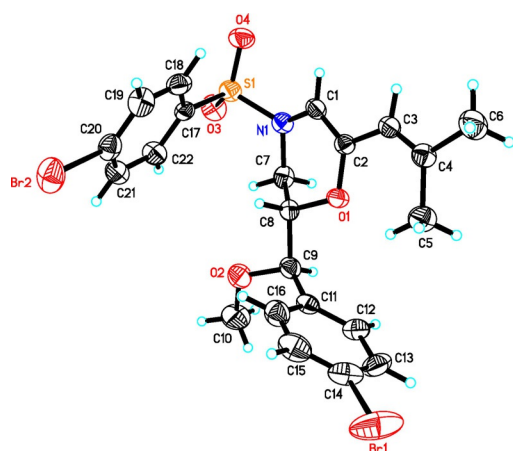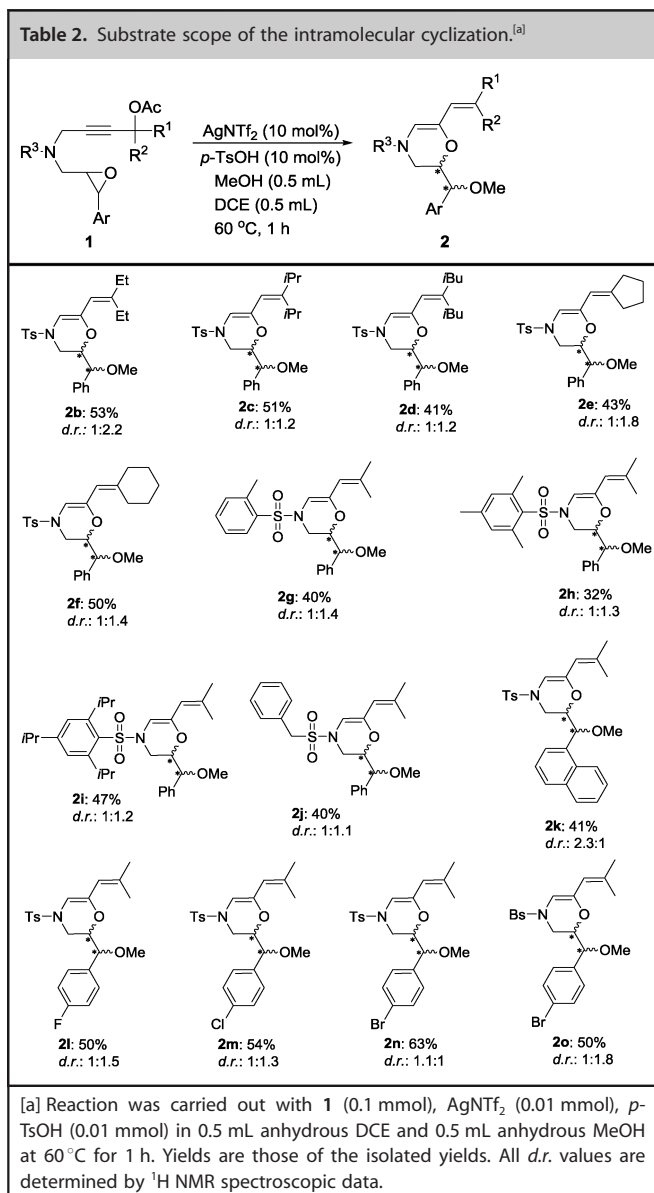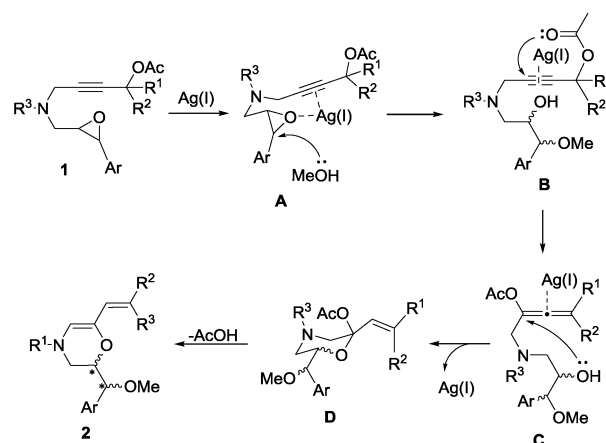
Table 2. Substrate scope of the intramolecular cyclization.[a]

2b: 53%
d.r.: 1:2.2

2c: 51%
d.r.: 1:1.2

2d: 41%
d.r.: 1:1.2

2e: 43%
d.r.: 1:1.8

2f: 50%
d.r.: 1:1.4

2g: 40%
d.r.: 1:1.4

2h: 32%
d.r.: 1:1.3

2i: 47%
d.r.: 1:1.2

2j: 40%
d.r.: 1:1.1

2k: 41%
d.r.: 2.3:1

2l: 50%
d.r.: 1:1.5

2m: 54%
d.r.: 1:1.3

2n: 63%
d.r.: 1.1:1

2o: 50%
d.r.: 1:1.8

[a] Reaction was carried out with **1** (0.1 mmol), AgNTf$_2$ (0.01 mmol), p-TsOH (0.01 mmol) in 0.5 mL anhydrous DCE and 0.5 mL anhydrous MeOH at 60 °C for 1 h. Yields are those of the isolated yields. All d.r. values are determined by ^{1}H NMR spectroscopic data.

Scheme 2. A plausible mechanism for the formation of **2**.

1,4-oxazine intermediate **D**. The subsequent intramolecular elimination of HOAc affords the corresponding product **2**. However, the alternative simple 6-*exo* addition/elimination process is also possible for this step.

Two control experiments were performed. One control was conducted by treating **1 a** under the optimized reaction condition in the absence of silver(I) catalyst, only affording the corresponding ring-opening product, and another control experiment used propargylic ether instead of propargylic acetate to carry out the reaction, but no desired product was obtained under the standard condition (Scheme 3); for the more detailed information, see the Supporting Information.
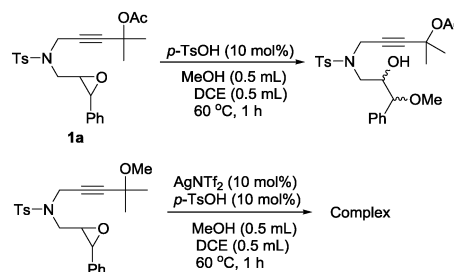
Scheme 3. The two control experiments that were performed.

Thus far, the synthesis of six-membered 1,4-oxazine derivatives have drawn much attention from organic chemists, because they exist in various natural products and possess significant biological and medicinal activities.[12] For instance, amorolfine **3** and several 1,4-benzoxazinones derivatives **4** are efficient antifungal agents, and amorolfine is already commercialized and sold in the drug market. The antiphlogistic, antipyretic, and analgesic effects of 4-aminoalkyl-2,3-dihydro-1,4-benzoxazin-3-ones **5** led to the proposed use of some of these compounds as efficient pharmaceuticals (Figure 2). Our new synthetic method for the preparation of **2** may provide an alternative method for the synthesis of these core structures in **3**–**5** upon further transformation.

In conclusion, we have developed an interesting silver(I)-catalyzed intramolecular cyclization of N-tethered epoxide-propar-
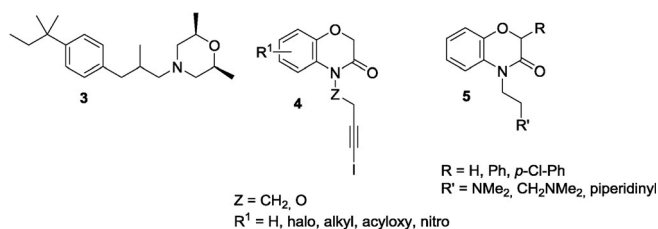

Figure 1. ORTEP drawing of *anti*-**2 o**.

Figure 2. Biologically active 1,4-oxazine derivatives.

gylic esters for the construction of a variety of 1,4-oxazine derivatives through a novel domino pathway consisting of three-membered ring-opening, 3,3-sigmatropic rearrangement, 6-*exo*-cycloisomerization, and subsequent intramolecular elimination under mild conditions. Further investigation into the mechanism and the extension and modification of this procedure to the synthesis of other heterocycles are under way in our laboratory.

Acknowledgements

[1] For recent selected reviews of gold catalysis, see: a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3221; b) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; *Angew. Chem.* **2007**, *119*, 3478–3519; c) V. Michelet, P. Y. Toullec, J. P. Genêt, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315; *Angew. Chem.* **2008**, *120*, 4338–4386; d) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350; e) Z. Li, C. Brower, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; f) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; g) D. J. Gorin, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; h) S. M. Abu Sohel, R.-S. Liu, *Chem. Soc. Rev.* **2009**, *38*, 2269–2281; i) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221; j) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241; *Angew. Chem.* **2010**, *122*, 5360–5369; k) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994–2009; l) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria, A. Simonneau, *Chem. Rev.* **2011**, *111*, 1954–1993; m) D. B. Huple, S. Ghorpade, R.-S. Liu, *Adv. Synth. Catal.* **2016**, *358*, 1348–1367. For recent selected reviews of silver catalysis, see: n) S. Díez-González, S. P. Nolan, *Acc. Chem. Res.* **2008**, *41*, 349–358; o) Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3199–3222; p) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev.* **2008**, *108*, 3174–3198; q) G. Fang, X. Bi, *Chem. Soc. Rev.* **2015**, *44*, 8124–8173; r) R. Karmakar, D. Lee, *Chem. Soc. Rev.* **2016**, *45*, 4459–4470; s) K. Sekine, T. Yamada, *Chem. Soc. Rev.* **2016**, *45*, 4524–4532.

[2] For early milestones, see: a) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem. Int. Ed.* **2000**, *39*, 2285–2288; *Angew. Chem.* **2000**, *112*, 2382–2385; b) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554. For a recent review, see: c) J. Xiao, X. Li,

Angew. Chem. Int. Ed. **2011**, *50*, 7226–7236; *Angew. Chem.* **2011**, *123*, 7364–7375.

[3] For selected examples of cyclization of epoxy alkynes, see: a) C. M. Marson, A. Khan, J. McGregor, T. J. Grinter, *Tetrahedron Lett.* **1995**, *36*, 7145–7148; b) A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859; c) F. E. McDonald, C. C. Schultz, *J. Am. Chem. Soc.* **1994**, *116*, 9363–9364; d) A. Fürstner, M. Méndez, *Angew. Chem. Int. Ed.* **2003**, *42*, 5355–5357; *Angew. Chem.* **2003**, *115*, 5513–5515; e) C. Molinaro, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 8076–0877; f) R. J. Madhushaw, M.-Y. Lin, S. M. A. Sohel, R.-S. Liu, *J. Am. Chem. Soc.* **2004**, *126*, 6895–6899; g) A. S. K. Hashmi, P. Sinha, *Adv. Synth. Catal.* **2004**, *346*, 432–438; h) C. Deutsch, B. H. Lipshutz, N. Krause, *Angew. Chem. Int. Ed.* **2007**, *46*, 1650–1653; *Angew. Chem.* **2007**, *119*, 1677–1681; i) A. S. K. Hashmi, M. Bührle, R. Salathé, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 2059–2064; j) M.-C. Cordonnier, A. Blanc, P. Pale, *Org. Lett.* **2008**, *10*, 1569–1572; k) G.-Y. Lin, C.-W. Li, S.-H. Hung, R.-S. Liu, *Org. Lett.* **2008**, *10*, 5059–5062; l) S. N. Karad, S. Bhunia, R.-S. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 8722–8726; *Angew. Chem.* **2012**, *124*, 8852–8856; m) C. Z. Rotsides, C. Hu, K. A. Woerpel, *Angew. Chem. Int. Ed.* **2013**, *52*, 13033–13036; *Angew. Chem.* **2013**, *125*, 13271–13274; n) S. K. Pawar, D. Vasu, R.-S. Liu, *Adv. Synth. Catal.* **2014**, *356*, 2411–2416; o) R. L. Sahani, R.-S. Liu, *Chem. Commun.* **2016**, *52*, 7482–7485.

[4] C. Gronnier, S. Kramer, Y. Odabachian, F. Gagosz, *J. Am. Chem. Soc.* **2012**, *134*, 828–831.

[5] L.-Z. Dai, M.-J. Qi, Y.-L. Shi, X.-G. Liu, M. Shi, *Org. Lett.* **2007**, *9*, 3191–3194.

[6] a) M. Shi, L.-P. Liu, J. Tang, *Org. Lett.* **2006**, *8*, 4043–4046; b) J.-M. Yang, Z. Zhang, Y. Wei, M. Shi, *Tetrahedron Lett.* **2012**, *53*, 6173–6176; c) J.-M. Yang, X.-Y. Tang, M. Shi, *Chem. Eur. J.* **2015**, *21*, 4534–4540; d) P.-L. Zhu, X.-Y. Tang, M. Shi, *ChemistryOpen* **2016**, *5*, 33–37.

[7] a) A. S. K. Hashmi, M. Rudolph, J. Huck, W. Frey, J. W. Bats, M. Hamzić, *Angew. Chem. Int. Ed.* **2009**, *48*, 5848–5852; *Angew. Chem.* **2009**, *121*, 5962–5966; b) A. S. K. Hashmi, S. Pankajakshan, M. Rudolph, E. Enns, T. Bander, F. Rominger, W. Frey, *Adv. Synth. Catal.* **2009**, *351*, 2855–2875; c) A. Zeiler, M. J. Ziegler, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Adv. Synth. Catal.* **2015**, *357*, 1507–1514.

[8] S. Bay, A. Englert, K. S. Nalivela, A. S. K. Hashmi, M. H. Larsen, *J. Organomet. Chem.* **2015**, *795*, 58–62.

[9] V. Belting, N. Krause, *Org. Lett.* **2006**, *8*, 4489–4492.

[10] CCDC 873624 (*anti*-**2o**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. Empirical Formula: $C_{22}H_{23}Br_2NO_4S$; Formula Weight: 557.29; Crystal Color, Habit: colorless, Crystal Dimensions: $0.256 \times 0.211 \times 0.145$ mm^3; Crystal System: Triclinic; Lattice Parameters: $a = 9.9064(18)$ Å, $b = 11.629(2)$ Å, $c = 11.711(2)$ Å, $\alpha = 106.775(4)°$, $\beta = 110.515(4)°$, $\gamma = 99.610(4)°$, $V = 1154.5(4)$ Å^3; Space group: P-1; $Z = 2$; $D_{calc} = 1.603$ g cm^{-3}; $F_{000} = 560$; Final R indices [$I > 2$ sigma(I)] R1 = 0.0584, wR2 = 0.1586.

[11] a) D. Leboeuf, A. Simonneau, C. Aubert, M. Malacria, V. Gandon, L. Fensterbank, *Angew. Chem. Int. Ed.* **2011**, *50*, 6868–6871; *Angew. Chem.* **2011**, *123*, 7000–7003; b) T. Fukuyama, Y. Ohta, C. Brancour, K. Miyagawa, I. Ryu, A. Dhimane, L. Fensterbank, M. Malacria, *Chem. Eur. J.* **2012**, *18*, 7243–7247; c) S. Kikuchi, S. Sekine, T. Ishida, T. Yamada, *Angew. Chem. Int. Ed.* **2012**, *51*, 6989–6992; *Angew. Chem.* **2012**, *124*, 7095–7098; d) Z. Zhang, M. Shi, *Chem. Eur. J.* **2012**, *18*, 3654–3658.

[12] a) G. Sun, P. S. Savle, R. D. Gandour, N. N. a'Bhaírd, R. R. Ramsay, F. R. Fronczek, *J. Org. Chem.* **1995**, *60*, 6688–6695; b) F. A. Macías, D. Marín, A. O. Bastidas, J. M. G. Molinillo, *Nat. Prod. Rep.* **2009**, *26*, 478–489; c) F. A. Macías, N. Chinchilla, E. Arroyo, J. M. G. Molinillo, D. Marín, R. M. Varela, *J. Agric. Food Chem.* **2010**, *58*, 2047–2053; d) N. A. Lack, P. A. -Cilies, P. Tavassoli, F. Q. Han, K. H. Chan, C. Feau, E. LeBlanc, E. T. Guns, R. K. Guy, P. S. Rennie, A. Cherkasov, *J. Med. Chem.* **2011**, *54*, 8563–8573.