

# Gold(I)/Copper(II)-Cocatalyzed Tandem Cyclization/Semipinacol Reaction: Construction of 6-Aza/Oxa-Spiro[4.5]decane Skeletons and Formal Synthesis of ( $\pm$ )-Halichlorine

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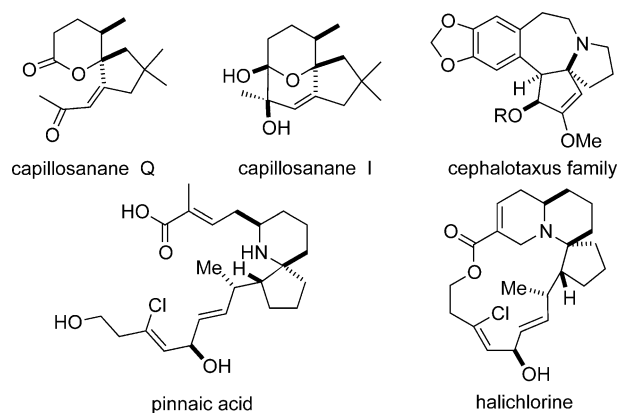
**Abstract:** A simple and efficient strategy for the construction of 6-*aza/oxa*-spiro[4.5]decane skeletons under the cocatalysis of gold(I)/copper(II) was developed, and its potential utility was demonstrated by a formal synthesis of the biologically active marine alkaloid ( $\pm$ )-halichlorine.

**Keywords:** cocatalysis; copper; gold; marine alkaloid; spirocycle

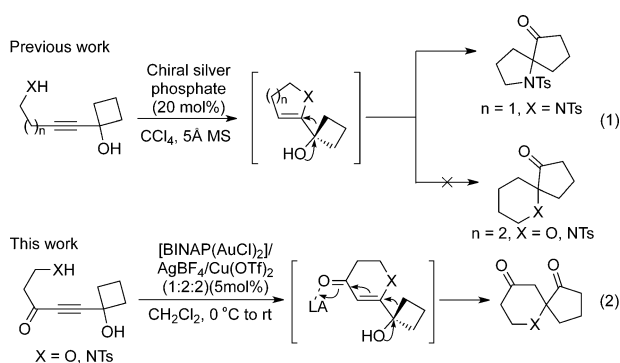
The development of strategies for the efficient construction of complex molecular skeletons is consistently a popular topic in the synthetic community.<sup>[1]</sup> Especially with the rapid development of certain disciplines such as chemical biology and pharmaceutical chemistry, and the appearance of modern techniques,<sup>[2]</sup> there has been significant growth in the demand for bioactive natural products and their derivatives. *Aza/oxa*-spirocyclic skeletons, as key structural moieties, broadly exist in a number of bioactive natural products, such as capillosanane Q,<sup>[3]</sup> capillosanane I,<sup>[3]</sup> cephalotaxin,<sup>[4]</sup> pinnaic acid,<sup>[5]</sup> and halichlorine<sup>[6,7]</sup> (Figure 1). Because of the special bioactivity and structural complexity of these molecules, particularly their potential for future drug discovery, strategies toward the syntheses of the relevant *aza/oxa*-spirocyclic skeletons have attracted the attention of organic chemists. Therefore, a variety of methodologies has been developed.<sup>[8,9]</sup> Among these methodologies, a stepwise introduction of the required *aza/oxa*-tetra-substituted-carbon center and the spirocyclic system has generally been employed. Few reports are available for a more straightforward strategy that affords the corresponding *aza/oxa*-spirocyclic skeleton in

a single step.<sup>[10–12]</sup> Selected examples for the construction of the *aza*-spiro[4.5]decane moiety include an addition/dipolar cycloaddition developed by Padwa's group, and Kibayashi's intramolecular ene reaction.<sup>[10,11]</sup> Therefore, the exploration for an alternative efficient approach for the synthesis of the spirocyclic scaffold remains highly desirable.

Because of our fascination with these structures, and our long-standing interest in the total synthesis of natural products using the semipinacol reaction,<sup>[13,14]</sup> we have previously developed a tandem intramolecular hydroamination/semipinacol rearrangement, which has been successfully applied to the formal synthesis of (–)-cephalotaxine (eq. 1 in Scheme 1).<sup>[15]</sup> However, this method is only effective for the synthesis of the *aza*-spiro[4.4]nonane skeleton, and the attempts for the construction of another important type of spiro-skeleton, i.e., 6-*aza/oxa*-spiro[4.5]decane, have failed. Based on the experimental results, we envisioned that the appropriate introduction of a carbonyl group in



**Figure 1.** Natural Products Containing *Oxa/Aza*-Spiro Structures.



**Scheme 1.** Tandem Cyclization/Semipinacol Reactions.

the substrates might facilitate the expected cyclization/rearrangement process through a dual-activation mode, therefore providing an alternative strategy for the synthesis of the related natural products. In this study, we present our research results of this methodology and its application in the formal synthesis of ( $\pm$ )-halichlorine (eq. 2 in Scheme 1).<sup>[7]</sup>

We commenced our investigation with compound **1a** as the model substrate. As shown in Table 1, in the initial tests using common  $\pi$ -acids, such as AuCl and PtCl<sub>2</sub>, only the use of AuCl could afford the desired spirocyclic product **2a** in a very low yield of 9%, and most of **1a** was recovered.<sup>[16]</sup> Fortunately, when [PPh<sub>3</sub>AuCl]/AgOTf (1:1) was used as the catalyst, **2a** could be obtained in a slightly higher yield of 15%. Based on this information and our previous experience with the semipinacol type vinylogous  $\alpha$ -ketol rearrangements,<sup>[17]</sup> we assumed that the presence of another Lewis/Brønsted acid might better promote the reaction by coordinating to the carbonyl group ultimately leading to a better outcome. Following this speculation, we observed that the addition of *p*-TsOH (10 mol%) into the reaction system clearly improved the yield of **2a**, and the use of *p*-TsOH/[PPh<sub>3</sub>AuCl]/AgBF<sub>4</sub> (1:1:1) gave a yield of 28% in CH<sub>2</sub>Cl<sub>2</sub>. Additionally, the reactivity difference between AuCl and [PPh<sub>3</sub>AuCl]/AgOTf (1:1) further prompted the evaluation of the corresponding ligand effect.<sup>[18]</sup> Accordingly, it was found that changing the ligand to BINAP could further increase the yield of **2a** to 47%. Intrigued by these results, we tested the combination of [(BINAP)(AuCl)<sub>2</sub>]/AgOTf (1:2) along with different Lewis acids as the catalyst. Among the catalysts applied, the use of [(BINAP)(AuCl)<sub>2</sub>]/AgBF<sub>4</sub>/Cu(OTf)<sub>2</sub> (1:2:2) resulted in the best yield of 69%.<sup>[19]</sup> Moreover, increasing the catalyst loading to 0.15 equiv did not significantly affect the yield, whereas decreasing the amount of the catalyst to 0.05 equiv clearly led to a lower yield (60%). Note that **2a** was not detected with Cu(OTf)<sub>2</sub> as the sole catalyst. Additionally, a solvent effect was observed for this reaction. Among the solvents screened, the use of toluene and CHCl<sub>3</sub> gave **2a** in a 38% and 45% yield, respectively. In contrast,

**Table 1.** Optimization of the Reaction Conditions.<sup>[a]</sup>

Entry	Catalyst	T [h]	Yield [%] <sup>[b]</sup>
1	AuCl	8	9
2	PtCl <sub>2</sub>	8	0
3	[PPh <sub>3</sub> AuCl]/AgOTf(1:1)	8	15
4	[PPh <sub>3</sub> AuCl]/AgOTf/ <i>p</i> -TsOH(1:1:1)	8	25
5	[(BINAP)(AuCl) <sub>2</sub> ]/AgBF <sub>4</sub> / <i>p</i> -TsOH(1:2:2)	8	28
6	[(BINAP)(AuCl) <sub>2</sub> ]/AgOTf/ <i>p</i> -TsOH(1:2:2)	8	41
7	[(BINAP)(AuCl) <sub>2</sub> ]/AgBF <sub>4</sub> / <i>p</i> -TsOH(1:2:2)	8	47
8	[(BINAP)(AuCl) <sub>2</sub> ]/AgBF <sub>4</sub> /Sc(OTf) <sub>3</sub> (1:2:2)	8	62
9	[(BINAP)(AuCl) <sub>2</sub> ]/AgBF <sub>4</sub> /In(OTf) <sub>3</sub> (1:2:2)	8	66
10	[(BINAP)(AuCl) <sub>2</sub> ]/AgBF <sub>4</sub> /Cu(OTf) <sub>2</sub> (1:2:2)	12	69
11 <sup>[c]</sup>	[(BINAP)(AuCl) <sub>2</sub> ]/AgBF <sub>4</sub> /Cu(OTf) <sub>2</sub> (1:2:1)	12	60
12 <sup>[d]</sup>	[(BINAP)(AuCl) <sub>2</sub> ]/AgBF <sub>4</sub> /Cu(OTf) <sub>2</sub> (1:2:3)	12	67
13	Cu(OTf) <sub>2</sub>	12	0
14 <sup>[e]</sup>	[(BINAP)(AuCl) <sub>2</sub> ]/AgBF <sub>4</sub> /Cu(OTf) <sub>2</sub> (1:2:2)	12	0
15 <sup>[f]</sup>	[(BINAP)(AuCl) <sub>2</sub> ]/AgBF <sub>4</sub> /Cu(OTf) <sub>2</sub> (1:2:2)	12	38
16 <sup>[g]</sup>	[(BINAP)(AuCl) <sub>2</sub> ]/AgBF <sub>4</sub> /Cu(OTf) <sub>2</sub> (1:2:2)	18	45

<sup>[a]</sup> Reaction conditions: **1a** (0.1 mmol), catalyst (5 mol%), and CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) stirred at °C under an argon atmosphere for 1 h, and then warmed to room temperature until full consumption of **1a**. *p*-TsOH = *p*-toluenesulfonic acid.

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup> [(BINAP)(AuCl)<sub>2</sub>]/AgBF<sub>4</sub>/Cu(OTf)<sub>2</sub> (1:2:1) (5 mol%).

<sup>[d]</sup> [(BINAP)(AuCl)<sub>2</sub>]/AgBF<sub>4</sub>/Cu(OTf)<sub>2</sub> (1:2:3) (5 mol%).

<sup>[e]</sup> THF (1.0 mL) instead of CH<sub>2</sub>Cl<sub>2</sub>.

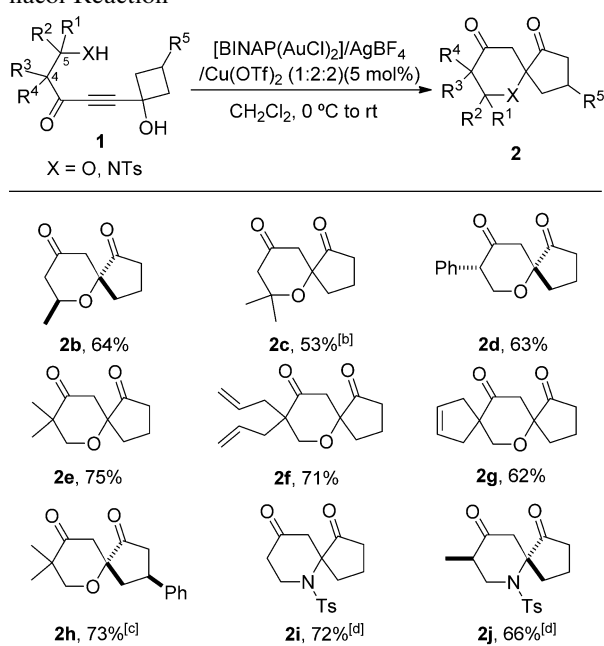
<sup>[f]</sup> Toluene (1.0 mL) instead of CH<sub>2</sub>Cl<sub>2</sub>.

<sup>[g]</sup> CHCl<sub>3</sub> (1.0 mL) instead of CH<sub>2</sub>Cl<sub>2</sub>.

when THF was used as the solvent, only substrate **1a** was recovered from the reaction system.

With the determination of the optimized conditions (Table 1, entry 10), we examined the generality of this tandem reaction. As summarized in Table 2, a variety of 6-*aza*/oxa-spiro[4.5]decanes could be obtained from the corresponding propargyl alcohols using this method. In the case of the 5-hydroxy-1-(1-hydroxycyclobutyl) pent-1-yn-3-ones, compounds with substituents at the C-5 position, which is closer to the reaction site, the change from the mono-methyl (**1b**) to the geminal dimethyl substitution (**1c**) reduced the re-

**Table 2.** Substrate Scope of the Tandem Cyclization/Semipinacol Reaction<sup>[a]</sup>



<sup>[a]</sup> Reaction conditions: **1** (0.09–0.74 mmol), (5 mol %) [BINAP(AuCl)<sub>2</sub>]/AgBF<sub>4</sub>/Cu(OTf)<sub>2</sub>(1:2:2) in CH<sub>2</sub>Cl<sub>2</sub> (0.1–0.75 mL) stirred at 0 °C for 1 h and then stirred at room temperature for 11 h for an isolated yield.

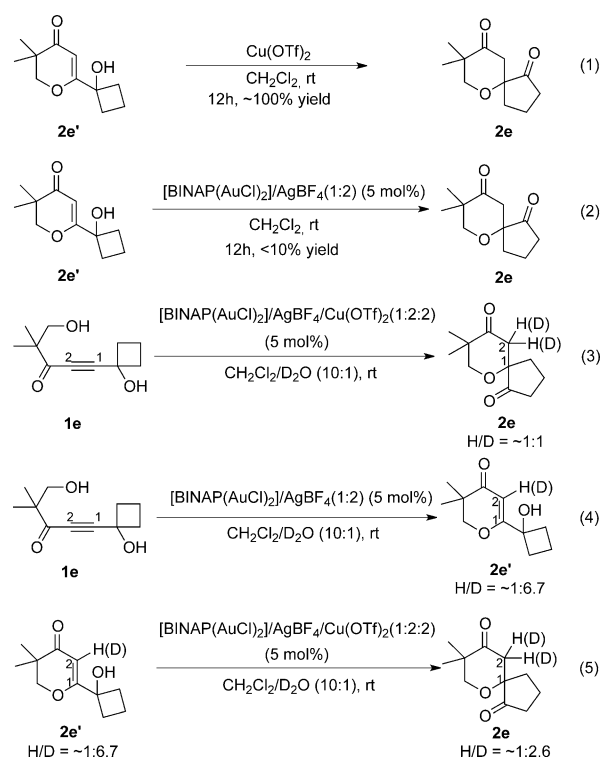
<sup>[b]</sup> For 120 h.

<sup>[c]</sup> Refluxed for 24 h.

<sup>[d]</sup> At –15 °C for 1 h, and then stirred at room temperature for 11 h.

action yield from 64% to 53% because of the possible existence of steric hindrance (Table 2, products **2b** vs. **2c**). In contrast, the substituents at the C-4 position did not significantly affect the yield. Substrates with a phenyl (**1d**), geminal dimethyl (**1e**) or geminal diallyl group (**1f**) at the C-4 position afforded the desired products in a good yield. Meanwhile, when the geminal dialkyl substituents were replaced by a cyclopent-3-enyl moiety, the expected product was also isolated in good yield. In addition, the substrate scope could be further expanded to the compounds with a nitrogen atom as the nucleophilic center leading to the efficient construction of the 6-aza-spiro[4.5]decane skeleton. Therefore, the subsection of substrates **1i** and **1j** to the standard reaction conditions produced the expected products **2i** (72% yield) and **2j** (66% yield), respectively. Note that the reaction exhibited excellent diastereoselectivity for the substrates **1b**, **1d**, **1h** and **1j** to give the corresponding products as single diastereoisomers.<sup>[20]</sup>

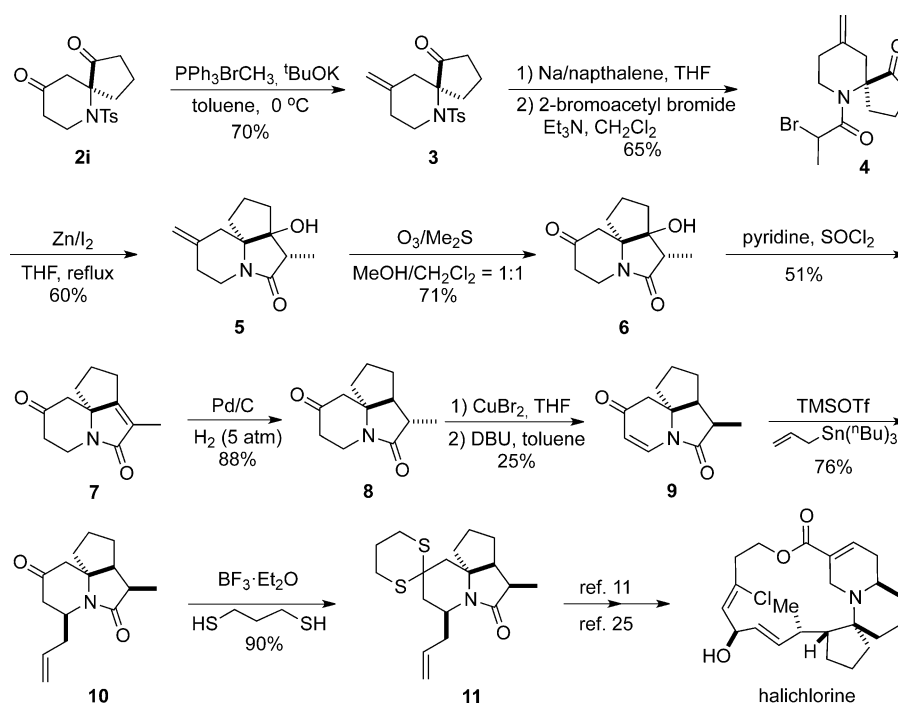
Besides, for some substrates, like **1e**, we could isolate the reaction intermediate **2e'**, which could be converted to the desired product **2e** in nearly quantitative yield under the catalysis of Cu(OTf)<sub>2</sub> (Scheme 2, eq. 1). While treatment of **2e'** with [(BI-



**Scheme 2.** Preliminary mechanistic studies.

NAP)(AuCl)<sub>2</sub>]/AgOTf (1:2) only gave **2e** in very low yield (eq. 2). Also, the reaction was carried out with CH<sub>2</sub>Cl<sub>2</sub>/D<sub>2</sub>O (10:1) as solvent. Although the reaction rate and yield were significantly affected in the presence of D<sub>2</sub>O, we could eventually manage to get the product **2e** with a H/D ratio of ~1:1 at 2-position (eq. 3). Additionally, intermediate **2e'** was obtained with a H/D ratio of ~1:6.7 at 2-position without the use of Cu(OTf)<sub>2</sub> (eq. 4). Moreover, in the same solvent, such an intermediate **2e'** could be transformed to **2e** with a H/D ratio of ~1:2.6 (eq. 5) at 2-position. All of these results supported the initial design of such a tandem reaction (Scheme 1, eq. 2). Additionally, the use of Cu(OTf)<sub>2</sub> might more efficiently promote the rearrangement of reaction intermediate via the activation of corresponding carbonyl group.

Encouraged by our experimental results, particularly the successful synthesis of *aza*-spiro-ketone **2i**, we attempted the synthesis of a corresponding natural product with this methodology to demonstrate its utility. Therefore, halichlorine, a representative bioactive marine alkaloid, was chosen as the target molecule.<sup>[7]</sup> The corresponding formal synthesis was started with compound **2i**, and primarily focused on the introduction of the required stereocenters to the spirocyclic skeleton (Scheme 3). Because the carbonyl group on the piperidine ring would cause side reactions in the subsequent nucleophilic steps, it was initially protected through a Wittig reaction to give compound **3**, which could afford the amide **4** in a 65% yield in two



**Scheme 3.** Formal Synthesis of (±)-Halichlorine.

steps, i.e., deprotection of the Ts group and amidation with 2-bromoacetyl bromide. We encountered certain difficulties with the desired intramolecular Reformatsky reaction under the standard reaction conditions.<sup>[21]</sup> Among the solvents tested, such as toluene, 1,4-dioxane, dimethoxyethane and tetrahydrofuran, only tetrahydrofuran gave the desired product in a poor yield. We also attempted to use zinc chloride and zinc powder to further improve the yield of this reaction. Unfortunately, the desired product was not obtained except for the debromination product.<sup>[22]</sup> Fortunately, the expected intramolecular Reformatsky reaction proceeded smoothly to produce the tricyclic intermediate **5** in a 60% yield with iodine as the initiator.<sup>[23]</sup> Next, ozonolysis of the terminal olefin followed by dehydration provided amide **7** in a 36% yield in two steps.<sup>[24]</sup> The high-pressure hydrogenation conditions successfully transformed compound **7** into compound **8** in an 88% yield. A known three-step transformation method, to introduce the desired carbon-carbon double bond and a configuration reversion of the C-14 methyl, was successfully achieved to give amide **9**, although in a relatively low yield of 25%. Subsequently, intermediate **10** was obtained by a 1,4-addition of amide **9** with allylstannane. Finally, protection of the carbonyl group of **10** with propane-1,3-dithiol afforded amide **11**, an advanced intermediate reported by Padwa's group toward the synthesis of halichlorine, thus successfully completing the formal synthesis.<sup>[11,25]</sup>

In conclusion, a Au<sup>I</sup>/Cu<sup>II</sup>-cocatalyzed tandem cyclization/semipinacol reaction was successfully devel-

oped and applied in the formal synthesis of halichlorine.<sup>[7]</sup> This methodology not only further enriched the content of the semipinacol rearrangement but also provided an efficient method for the construction of the 6-aza/oxa-spiro[4.5]decane skeletons and the synthesis of the related natural products.

## Experimental Section

### General procedure:

AgBF<sub>4</sub> (1.9 mg, 0.01 mmol, 1 equiv) was added to a solution of [(BINAP)(AuCl)<sub>2</sub>] (5.6 mg, 0.005 mmol, 0.5 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL). After the reaction mixture was stirred for 2 h at room temperature, the catalyst [(BINAP)Au<sub>2</sub>(BF<sub>4</sub>)<sub>2</sub>] was obtained by filtering the mixture through a celite pad. Next, [(BINAP)(AuBF<sub>4</sub>)<sub>2</sub>] (0.005 mmol) and Cu(OTf)<sub>2</sub> (3.6 mg, 0.01 mmol) were added to a solution of 5-hydroxy-1-(1-hydroxycyclobutyl)pent-1-yn-3-one **1a** (16.8 mg, 0.1 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) under argon. After stirring for 1 h, the reaction mixture was allowed to warm to room temperature until the substrates disappeared. The reaction mixture was concentrated under vacuum. Purification of the residue by column chromatography on silica gel (petroleum/EtOAc = 10:1) provided the desired product.

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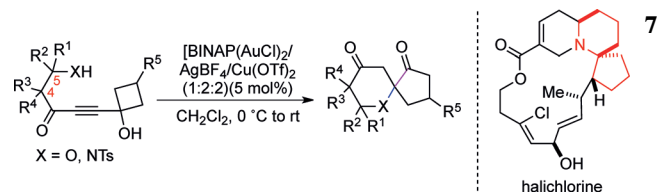
## References

- [1] a) P. A. Wender, *Chem. Rev.* **1996**, *96*, 1–2; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; c) J. Montgomery, *Angew. Chem.* **2004**, *116*, 3980–3998, *Angew. Chem. Int. Ed.* **2004**, *43*, 3890–3908; d) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292–7344, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; e) D. Enders, C. Grondal, R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; f) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167–178; g) J. Panteleev, L. Zhang, M. Lautens, *Angew. Chem.* **2011**, *123*, 9255–9258; *Angew. Chem. Int. Ed.* **2011**, *50*, 9089–9092.
- [2] a) K. S. Zachary, J.-P. Fu, W. Brigitte, *J. Med. Chem.* **2014**, *57*, 7145–7159; b) M. A. Johns, *ACS Chem. Biol.* **2012**, *7*, 14–19.
- [3] D.-A. Chen, W. Chen, D. Liu, L. Ofwegen, P. Proksch, *J. Nat. Prod.* **2013**, *76*, 1753–1763.
- [4] S. M. Weinreb, M. F. Semmelhack, *Acc. Chem. Res.* **1975**, *8*, 158–164.
- [5] T. Chou, M. Kuramoto, Y. Otani, M. Shikano, K. Yazawa, D. Uemura, *Tetrahedron Lett.* **1996**, *37*, 3871–3874.
- [6] a) M. Kuramoto, T. Chou, K. Yamada, T. Chiba, Y. Hayashi, D. Uemura, *Tetrahedron Lett.* **1996**, *37*, 3867–3870; b) S. Xu, D. Unabara, D. Uemura, H. Arimoto, *Chem. Asian J.* **2014**, *9*, 367–375.
- [7] For reviews, see: D. L. J. Clive, M.-L. Yu, J. Wang, V. S. C. Yeh, S.-Z. Kang, *Chem. Rev.* **2005**, *105*, 4483–4514.
- [8] For reviews, see a) E. Bialy, A. A. Serry, B. Holger, L. F. Tietze, *Synthesis* **2004**, 2249–2262; b) G. Dake, *Tetrahedron.* **2006**, *62*, 3467–3492.
- [9] For select *aza/oxa*-spirocycles examples, see: a) R. E. Ireland, P. Maienfisch, *J. Org. Chem.* **1988**, *53*, 640–651; b) S. M. Donald, N. S. Simpkins, *Tetrahedron* **1990**, *46*, 545–564; c) J. T. Negri, L. A. Paquette, *J. Am. Chem. Soc.* **1992**, *114*, 8835–8841; d) N. Noguchi, M. Nakada, *Org. Lett.* **2006**, *8*, 2039–2042; e) A. Adrien, H.-J. Gais, F. Köhler, J. Runsink, G. Raabe, *Org. Lett.* **2007**, *9*, 2155–2158; f) Z.-W. Jiao, S. Y. Zhang, C. He, Y.-Q. Tu, *Angew. Chem.* **2012**, *124*, 8941–8945, *Angew. Chem. Int. Ed.* **2012**, *51*, 8811–8815; g) P. Wipf, C. R. J. Stephenson, M. A. A. Walczak, *Org. Lett.* **2004**, *6*, 3009–3012; h) J.-A. Burkhand, B. Wagner, H. Fischer, S. Franz, K. Muller, E. M. Carreira, *Angew. Chem.* **2010**, *122*, 3603–3606; *Angew. Chem. Int. Ed.* **2010**, *49*, 3524–3527; i) K. J. Xiao, J.-M. Luo, X.-E. Xia, Y. Wang, P.-Q. Huang, *Chem. Eur. J.* **2013**, *19*, 13075–13086.
- [10] Y. Matsumura, S. Aoyagi, C. Kibayashi, *Org. Lett.* **2003**, *5*, 3249–3252.
- [11] A. C. Flick, M. J. A. Caballero, H. I. Lee, A. Padwa, *J. Org. Chem.* **2010**, *75*, 1992–1996.
- [12] a) L. I. Palmer, J. R. de Alaniz, *Angew. Chem.* **2011**, *123*, 7305–7308, *Angew. Chem. Int. Ed.* **2011**, *50*, 7167–7170; b) L. I. Palmer, J. R. de Alaniz, *Org. Lett.* **2013**, *15*, 476–479; c) X.-H. Ouyang, R.-J. Song, Y. Li, B. Liu, J.-H. Li, *J. Org. Chem.* **2014**, *79*, 4582–4589.
- [13] For some reviews, see: a) B. Rickborn, in: *Comprehensive Organic Synthesis, Vol. 3* (Eds: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 721; b) L. E. Overman, *Acc. Chem. Res.* **1992**, *25*, 352–359; c) T. J. Snape, *Chem. Soc. Rev.* **2007**, *36*, 1823–1842; d) B. Wang, Y.-Q. Tu, *Acc. Chem. Res.* **2011**, *44*, 1207–1222; e) Z.-L. Song, C.-A. Fan, Y.-Q. Tu, *Chem. Rev.* **2011**, *111*, 7523–7556; f) T. Seiser, T. Saget, D. N. Tran, N. Cramer, *Angew. Chem.* **2011**, *123*, 7884–7896; *Angew. Chem. Int. Ed.* **2011**, *50*, 7740–7752; g) E. Leemans, M. D'hooghe, N. De Kimpe, *Chem. Rev.* **2011**, *111*, 3268–3333; h) S.-H. Wang, B.-S. Li, Y.-Q. Tu, *Chem. Commun.* **2014**, *50*, 2393–2408; i) S.-H. Wang, Y.-Q. Tu, in: *Comprehensive Organic Synthesis II, Vol. 3* (Eds: G. A. Molander, P. Knochel), Pergamon, Oxford, **2014**, pp. 795–852.
- [14] a) T. C. Coombs, Y.-Q. Zhang, E. C. Garnier-Amblard, L. S. Liebeskind, *J. Am. Chem. Soc.* **2009**, *131*, 876–877; b) Z.-H. Chen, Z.-M. Chen, Y.-Q. Zhang, Y.-Q. Tu, F.-M. Zhang, *J. Org. Chem.* **2011**, *76*, 10173–10186; c) H.-Y. Lee, C.-K. Sha, *J. Org. Chem.* **2012**, *77*, 598–605; d) D. J. Canham, L. E. Overman, *J. Org. Chem.* **2013**, *78*, 9–34; e) M.-C. P. Yeh, M.-N. Lin, C.-H. Hsu, C.-J. Liang, *J. Org. Chem.* **2013**, *78*, 12381–12396.
- [15] Q.-W. Zhang, K. Xiang, Y.-Q. Tu, S.-Y. Zhang, X.-M. Zhang, Y.-M. Zhao, T.-C. Zhang, *Chem. Asian J.* **2012**, *7*, 894–898.
- [16] a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; b) A. S. K. Hashmi, L. Grundl, *Tetrahedron* **2005**, *61*, 6231–6236; c) D.-W. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X.-B. Liu, J. L. Petersen, X.-D. Shi, *J. Am. Chem. Soc.* **2012**, *134*, 9012–9019; d) Y.-F. Chen, L. Wang, N. Sun, X. Xie, X.-B. Zhou, H.-Y. Chen, Y.-X. Li, Y.-H. Liu, *Chem. Eur. J.* **2014**, *20*, 12015–12019; e) T. Wang, S. Shi, M. Rudolph, A. S. K. Hashmi, *Adv. Synth. Catal.* **2014**, *356*, 2337–2342; f) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766–1775; g) A. S. K. Hashmi, *Chem. Soc. Rev.* **2012**, *41*, 2448–2462; h) M. Gaydou, R. E. Miller, N. Delpont, J. Cecon, A. M. Echavarren, *Angew. Chem.* **2013**, *125*, 6524–6527, *Angew. Chem. Int. Ed.* **2013**, *52*, 6396–6399; i) J. Carerras, M. Livendahl, P. R. McGonigal, A. M. Echavarren, *Angew. Chem.* **2014**, *126*, 4996–4999, *Angew. Chem. Int. Ed.* **2014**, *53*, 4896–4899; j) C. Obradors, A. M. Echavarren, *Acc. Chem. Res.* **2014**, *47*, 902–912.
- [17] E. Zhang, C.-A. Fan, Y.-Q. Tu, F.-M. Zhang, Y.-L. Song, *J. Am. Chem. Soc.* **2009**, *131*, 14626–14627.
- [18] a) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; b) J. A. Gillespie, E. Zuidema, P. W. N. M. van Leeuwen, P. C. J. Kamer, in: *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis* (Eds.: P. C. J. Kamer, P. W. N. M. Van Leeuwen), Wiley, Chichester, **2012**, pp. 1–26; c) A. S. K. Hashmi, *Science* **2012**, *338*, 1434–1434; d) M. C. B. Jaimes, C. R. N. Bohling, J. M. Serrano-Becerra, A. S. K. Hashmi, *Angew. Chem.* **2013**, *125*, 8121–8124, *Angew. Chem. Int. Ed.* **2013**, *52*, 7963–7966; e) M. C. B. Jaimes, F. Rominger, M. M. Pereira, R. M. B. Carrilho,

- S. A. C. Carabineiro, A. S. K. Hashmi, *Chem. Commun.* **2014**, 50, 4937–4940.
- [19] a) C. Zhu, S.-M. Ma, *Org. Lett.* **2014**, 16, 1542–1545; b) D.-G. Yu, M. Suri, F. Glorius, *J. Am. Chem. Soc.* **2013**, 135, 8802–8805; c) Y.-P. Yan, P. Feng, Q.-Z. Zheng, Y.-F. Liang, J.-F. Lu, Y.-X. Cui, N. Jiao, *Angew. Chem.* **2013**, 125, 5939–5943, *Angew. Chem. Int. Ed.* **2013**, 52, 5827–5831.
- [20] The relative configuration was confirmed by X-ray crystallography. CCDC 1018381 (**2b**), CCDC 1001590 (**2d**), 1001591 (**2h**) and CCDC 1018382 (**2j-2**) 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](http://www.ccdc.cam.ac.uk/data_request/cif).
- [21] S. Reformatsky, “Neue Synthese zweiatomiger einbasischer Säuren aus den Ketonen”, *Ber. Dtsch. Chem. Ges.* **1887**, 20, 1210–1211.
- [22] a) C. H. Heathcock, J. C. Kath, R. B. Ruggeri, *J. Org. Chem.* **1995**, 60, 1120–1130; b) P. G. Cozzi, *Angew. Chem.* **2007**, 119, 2620–2623; *Angew. Chem. Int. Ed.* **2007**, 46, 2568–2571; c) H.-R. Xue, P. Gopal, J. Yang, *J. Org. Chem.* **2012**, 77, 8933–8945.
- [23] B. H. Han, P. Boudjouk, *J. Org. Chem.* **1982**, 47, 5030–5032.
- [24] a) K.-F. Hebenbrock, *Justus Liebigs Ann. Chem.* **1978**, 320–336; b) J.-B. Peng, X.-J. Hou, S.-Y. Zhang, Y.-Q. Tu, *Acta Chim. Sinica* **2012**, 70, 2232–2233.
- [25] a) K. S. Feldman, A. L. Perkins, K. M. Masters, *J. Org. Chem.* **2004**, 69, 7928–7932; b) Y. Matsumura, S. Aoyagi, C. Kibayashi, *Org. Lett.* **2004**, 6, 965–968; c) D. Trauner, J. B. Schwarz, S. J. Danishefsky, *Angew. Chem.* **1999**, 111, 3756–3758; *Angew. Chem. Int. Ed.* **1999**, 38, 3542–3545.

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