VIP Cyclotrimerization Very Important Paper

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[1+1+1] Cyclotrimerization for the Synthesis of Cyclopropanes

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Abstract: *The synthesis of small rings by functionalization of C(sp³)–H bonds remains a great challenge. We report for the first time a copper-catalyzed [1+1+1] cyclotrimerization of acetophenone derivatives under mild reaction conditions. The reaction has a broad scope for the stereoselective synthesis of cyclopropanes by trimerization of acetophenone. The developed transformation is based on an extraordinary copper-catalyzed cascade process that allows saturated carbocycles to be obtained for the first time by cyclotrimerization through functionalization of C(sp³)–H bonds. The cascade of sixfold C(sp³)–H bond functionalization allows the synthesis of cyclopropanes in a highly stereoselective approach.*

Intermolecular cyclotrimerization reactions are among the most efficient methods for the synthesis of complex products in a single step from simple nonfunctionalized building blocks.[1] The cyclotrimerization is expected to have outstanding potential because of is high atom economy, high product yields, and broad reaction scope. Efficient, selective, and practical procedures based on the [2+2+2] cyclotrimerization of alkynes were developed for the synthesis of polysubstituted benzenes (Figure 1 a).[2] Achievements in the regioselective formation of various benzenes resulted in the broad application of [2+2+2] cyclotrimerization for the synthesis of materials, drugs, and bioactive compounds.[2,3] The [2+2+2] cyclotrimerization of acetophenones provides a regioselective approach to polysubstituted aromatic compounds.[4] Those processes occur under mild reaction conditions and produce water as a by-product. However, known methods of cyclotrimerization only allow the synthesis of unsaturated carbocyclic compounds and the synthesis of fully saturated carbocycles has not been reported. The biggest problem for the synthesis of saturated carbocycles is associated with the possible formation of stereocenters, which would require a regio-, diastereo-, and stereoselective approach for the synthesis of target compounds. Here we demonstrate the first catalytic approach for the synthesis of small strained cyclopropanes by an unprecedented [1+1+1] cyclotrimerization of simple ketones. A notable feature of our approach is its high stereoselectivity and its extraordinary cascade of regioselective sixfold functionalization of unreactive C(sp³)–H bonds. Our results reveal a new method for the synthesis of cyclopropanes[5] and an unparalleled cascade reaction mechanism in which a single catalyst is used in several steps.

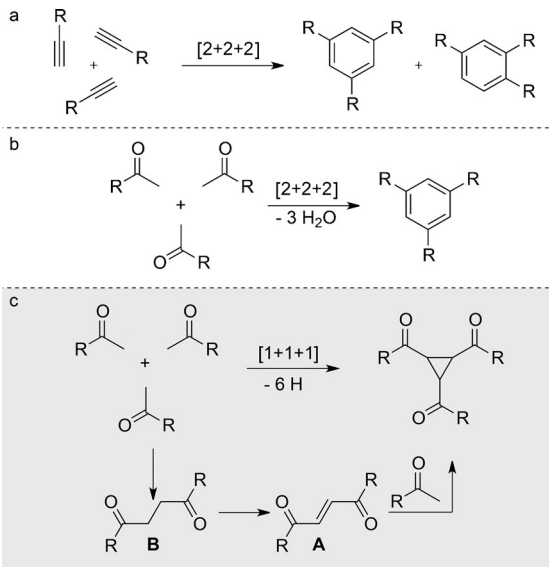

Figure 1. Cyclotrimerization. a) [2+2+2] Cyclotrimerization of acetylenes for the synthesis of benzene derivatives. b) [2+2+2] Cyclotrimerization of acetophenones for the synthesis of benzene derivatives. c) Present work: [1+1+1] cyclotrimerization of acetophenones for the synthesis of cyclopropane derivatives.

Having an interest in the development of novel oxidative coupling methods,[6,7] we envisaged that a novel approach for the synthesis of cyclopropanones could be realized through the cyclotrimerization of acetophenone under radical reaction conditions[6] (Figure 1 c). A radical addition of acetophenone to unsaturated diketone **A** could provide the desired cyclopropane. Intermediate **A** could be obtained from 1,4-diketone **B** under oxidative reaction condition. Furthermore, diketone **B** can be obtained by the oxidative coupling of ketones.[8] Therefore, we would need three molecules of ketones to create a small cycle.

To test our hypothesis, we began our study on the [1+1+1] cyclotrimerization of 4-fluoroacetophenone (**1a**) using CuI (10 mol %) in the presence of 2,2′-bipyridine-based ligands (Table 1, entries 1–6, and see Table S1 in the Supporting Information). To our delight, we observed a ligand-induced

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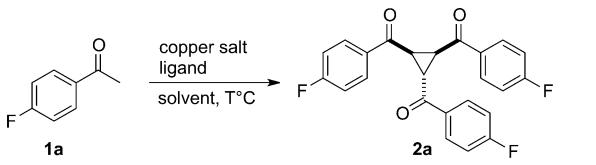
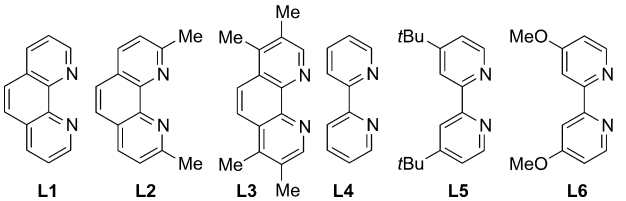
Table 1: Screening of reaction conditions.[a]





Entry	Cu salt (mol %)	Ligand (mol %)	Solvent	Oxidant (equiv)	Yield [%]
1	CuI (10)	**L1** (20)	PhCl	DTBP	traces
2	CuI (10)	**L2** (20)	PhCl	DTBP	traces
3	CuI (10)	**L3** (20)	PhCl	DTBP	traces
4	CuI (10)	**L4** (20)	PhCl	DTBP	41
5	CuI (10)	**L5** (20)	PhCl	DTBP	73
6	CuI (10)	**L6** (20)	PhCl	DTBP	55
7	CuI (10)	**L5** (20)	PhCl	DCP	55
8	CuI (10)	**L5** (20)	PhCl	TBHP	15
9	CuI (5)	**L5** (20)	PhCl	DTBP	48
10	CuBr (10)	**L5** (20)	PhCl	DTBP	68
11	CuCl (10)	**L5** (20)	PhCl	DTBP	72
12	$Cu(OAc)_2$ (10)	**L5** (20)	PhCl	DTBP	traces
13[b]	CuI (10)	**L5** (20)	PhCl	DTBP	86
14[b]	CuI (10)	**L5** (20)	PhMe	DTBP	traces
15[b]	CuI (20)	**L5** (20)	DMF	DTBP	43
16[b]	CuI (20)	**L5** (20)	PhF	DTBP	68
17[b]	CuI (20)	**L5** (20)	PhBr	DTBP	74

[a] Reaction conditions: **1a** (0.5 mmol), oxidant (3 equiv), copper salt (10 mol%), ligand (20 mol%) in solvent (2.0 mL) at 100°C for 8 h under argon [b] Reaction carried out at 90°C for 8 h. DTBP = di-*tert*-butyl peroxide, DCP = dicumyl peroxide, TBHP = *tert*-butyl hydrogen peroxide.

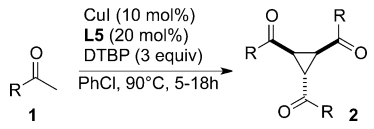
formation of the desired cyclopropane[9] **2a** in the presence of di-*tert*-butyl peroxide (DTBP) as an oxidant in chlorobenzene at 100°C under argon after 12 h. Pleasingly, we found that 4,4′-di-*tert*-butyl-2-2′-bipyridine (**L5**) was the best ligand for the copper-catalyzed cyclotrimerization of acetophenone **1a**. It is notable that the product of the [1+1+1] cyclotrimerization (**2a**) was formed as a single stereoisomer. Unfortunately, other nitrogen-containing ligands did not give promising results for the synthesis of **2a** (see Table S1). We then examined various oxidants. The yield of cyclopropane **2a** was reduced when dicumyl peroxide or *tert*-butyl hydroperoxide were used (Table 1, entries 7 and 8, and see Table S2). Furthermore, cyclotrimerization occurred when benzoyl peroxide, hydrogen peroxide, $K_2S_2O_8$, or (diacetoxyiodo)benzene were used as oxidants (see Table S2). The formation of product **2a** drastically decreased when air was used instead of argon. The highest yield of the desired product **2a** (73%) was obtained using DTBP (3 equiv). A reduction in the loading of CuI from 10 mol % to 5 mol % led to a decrease of **2a**.

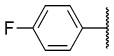
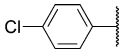
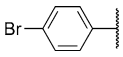
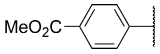
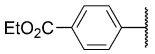
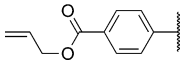
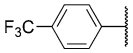
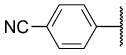
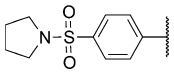
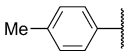
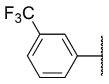
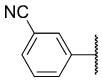
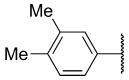
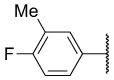
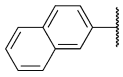
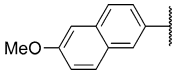
Various copper salts were examined to identify the best precatalyst (Table 1, entries 10–12 and Table S3). The yield of the cyclotrimerization product was reduced when various copper(I) salts were used. The application copper(II) salts as the precatalyst led to a further decrease in the product yield. Thus, subsequent cyclotrimerization reactions were performed in the presence of CuI. The effect of temperature was next examined. The yield of the desired product **2a** was increased to 86% on reduction of the reaction temperature from 100°C to 90°C (entry 13). However, a further decrease or increase in temperature led to a lower yield of **2a** (see Table S4). No formation of the target product was observed when polar solvents such as H_2O, *tert*-AmOH, or DMSO were used (entries 14–17 and see Table S5). Only the formation of trace amounts of product was observed in nonpolar solvents such as toluene and *p*-xylene. Aromatic halogenated solvents were found to be suitable for the [1+1+1] cyclotrimerization of acetophenones, with chlorobenzene found to be the best solvent for the synthesis of cyclopropanes.

With the optimized reaction conditions in hand, we next investigated the scope of the unprecedented copper-catalyzed [1+1+1] cyclotrimerization. We found that various acetophenones can be transformed into the corresponding products in moderate to good yields (Table 2). Interestingly, a wide array of functional groups such as halogens, carbonyl, sulfonamide, nitryl, alkoxy, and alkyl were tolerated under the optimized conditions (Table 2, entries 1–19). To our delight, various electron-withdrawing groups as well as electron-donating groups on the aryl moiety were tolerated. However, acetophenones with electron-withdrawing groups reacted faster than electron-rich derivatives. Furthermore, substitutions in the *ortho*-, *meta*-, and *para*- positions give comparable results under the developed reaction conditions. Polysubstituted acetophenones were also tested for the formation of the desired products. It is remarkable that heterocyclic derivatives such as 2-acetylthiophene were found to form the desired product in 52% yield under the developed oxidative reaction conditions (Table 2, entry 20). It is interesting that although the bond dissociation energies (BDEs) of all the methyl groups in 3,4-dimethylacetophenone are similar (BDE = 89–91 kcal mol^{-1}), the reaction occurs by functionalization of the methyl group attached to the carbonyl group (Table 2, entry 15). Moreover, the reaction with allyl 4-acetylbenzoate (Table 2, entry 6) gave the desired cyclopropane **2f** in moderate yield, despite a methylene group with a dramatically lower BDE being present (BDE = 81 kcal mol^{-1}). Therefore, the developed method allows the functionalization of a strong C(sp^3)–H bond in the presence of a weak one. Finally, we scaled-up the experiment using **1c** (6 mmol). Product **3c** was formed smoothly in the scaled-up experiment in a yield of 66%.

Following our synthetic studies, we performed a number of experiments to gain insight into the reaction mechanism of the copper-catalyzed [1+1+1] cyclotrimerization reaction. Based on the reaction design, we carried out control experiments using possible intermediates. Initially, we tested diketone **3**, which can be formed by the oxidative dimerization of acetophenones (Figure 2a).[10] Under optimized reaction conditions, diketone **3** reacts with acetophenone **1d** to afford cyclopropane **4** in good yield and regioselectivity. Moreover, under the same reaction conditions but in the

Table 2: Scope of the [1+1+1] cyclotrimerization.[a]



Entry	R	Product	*t* [h]	Yield [%]
1		**2a**	8	86
2		**2b**	8	66
3		**2c**	8	73
4		**2d**	8	88
5		**2e**	8	65
6		**2f**	6	43
7		**2g**	5	79
8		**2h**	6	62
9		**2i**	8	35
10		**2j**	8	43
11[b]		**2k**	12	69
12		**2l**	8	46
13		**2m**	7	68
14		**2n**	8	77
15[c]		**2o**	18	53
16		**2p**	18	43
17		**2q**	8	65
18[b]		**2r**	12	46
19		**2s**	8	41
20		**2t**	8	52

[a] Reaction conditions: **2** (0.5 mmol), DTBP (3 equiv), CuI (10 mol %), **L5** (20 mol %) in PhCl (2.0 mL) at 90 °C for 5–8 h under argon. Yields are given for isolated products. All products were formed with d.r. > 20:1. [b] CuI (20 mol %), **L5** (30 mol %) were used at 75 °C for 12 h under argon. [c] Reaction was carried out in 1 mL DMF for 18 h.

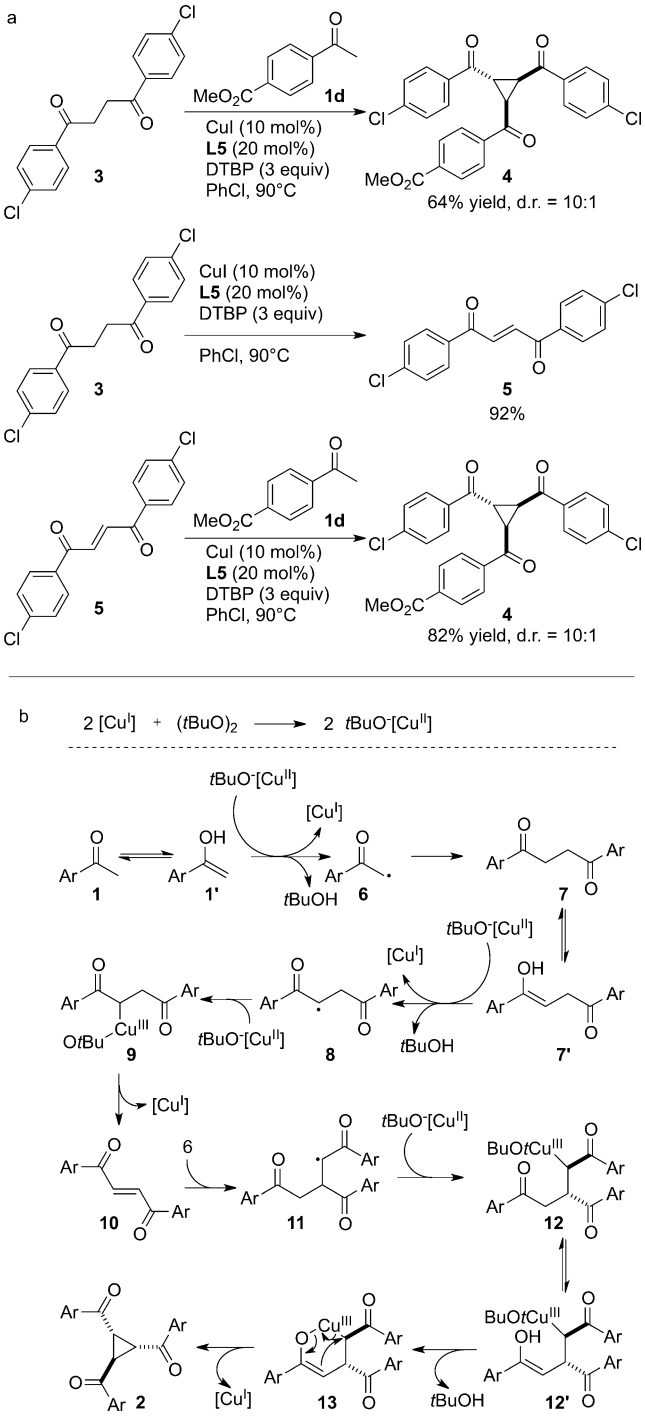


Figure 2. Studies on reaction mechanism and plausible reaction mechanism. a) Control experiments. b) Reaction mechanism.

absence of acetophenone **1d**, the unsaturated diketone **5** was formed in excellent yield from diketone **3**. The reaction of diketone **5** with acetophenone **1d** provided product **4** in high yield. Based on those experiments, we concluded that the [1+1+1] cyclotrimerization proceeds through the following reaction sequence: 1) dimerization of ketones to 1,4-diketones, 2) oxidation of 1,4-diketones to but-2-ene-1,4-dione, and 3) annulation of but-2-ene-1,4-dione with a third equivalent of acetophenone. The formation of cyclopropanes was suppressed in the presence of radical scavengers such as TEMPO under the optimized reaction conditions. Therefore, cyclotrimerization involves the formation of radical intermediates. However, the kinetic isotopic effect was the same at

1.4 (see the Supporting Information for details). Hence, the abstraction of any of the six hydrogen atoms is not the rate-limiting step. The use of trideuterated acetophenone ([D_3]-**1k**) in the cyclotrimerization resulted in the trideuterated product ([D_3]-**2k**), with a deuterium incorporation of $>95\%$. Therefore, the observed diastereoselectivity of the reaction is not a result of epimerization after formation of the cyclopropane.

On the basis of the above preliminary results, a plausible mechanism is shown in Figure 2b. Initially, the Cu^{II} complex is generated by oxidation of Cu^{I} in the presence of DTBP.[6,11] In the next step, acetophenone **1** is oxidized in its enol form **1′** by a Cu^{II} species to afford radical **6**. Subsequent dimerization of **6** leads to the formation of diketone **7**. Diketone **7** subsequently undergoes the next step of oxidation through its enol form **7′** to form radical **8**, which is trapped by the Cu^{II} species to form organocuprate **9**. Intermediate **9** then undergoes a β-hydride elimination to yield unsaturated diketone **10** with complete *trans* selectivity. Subsequent addition of radical **6** to **10** leads to the formation of radical **11**, which is trapped by the Cu^{II} species to form intermediate **12**. In a next step, **12** is converted into the key metallocycle **13** through ligand exchange of the enol form **12′**. Reductive elimination of the Cu^{I} species from intermediate **13** results in the stereoselective formation of cyclopropane **2**.

In conclusion, we have discovered an extraordinary [1+1+1] cyclotrimerization for the synthesis of cyclopropane rings. For the first time, cyclotrimerization was applied to the stereoselective synthesis of small saturated carbocycles from nonfunctionalized acetophenone derivatives. The discovery is based on an unprecedented copper-catalyzed cascade process. The cyclotrimerization showed broad scope. Mechanistic studies revealed the reaction had a novel radical pathway. This general catalytic [1+1+1] cyclotrimerization reaction allows direct access to the stereoselective synthesis of cyclopropanes and provides an inspiration for the development of novel methods for the synthesis of saturated carbocycles by cyclotrimerization.

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Keywords: copper · cyclopropanes · cyclotrimerization · oxidative coupling · radicals

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[1] a) M. Amatore, C. Aubert, *Eur. J. Org. Chem.* **2015**, 265–286; b) B. Heller, M. Hapke, *Chem. Soc. Rev.* **2007**, *36*, 1085–1094; c) R. P. Chopade, J. Louie, *Adv. Synth. Catal.* **2006**, *348*, 2307–2327; d) S. Kotha, E. Brahmachary, K. Lahiri, *Eur. J. Org. Chem.* **2005**, 4741–4767; e) J. A. Varela, C. Saa, *Chem. Rev.* **2003**, *103*, 3787–3801; f) K. P. C. Vollhardt, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 539–556; *Angew. Chem.* **1984**, *96*, 525–541; g) K. P. C. Vollhardt, *Acc. Chem. Res.* **1977**, *10*, 1–8.

[2] a) B. R. Galan, T. Rovis, *Angew. Chem. Int. Ed.* **2009**, *48*, 2830–2834; *Angew. Chem.* **2009**, *121*, 2870–2874; b) V. Gandon, C. Aubert, M. Malacria, *Chem. Commun.* **2006**, 2209–2217; c) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901–2915.

[3] a) N. Weding, M. Hapke, *Chem. Soc. Rev.* **2011**, *40*, 4525–4538; b) G. Domínguez, J. Pérez-Castells, *Chem. Soc. Rev.* **2011**, *40*, 3430–3444; c) K. Tanaka, *Chem. Asian J.* **2009**, *4*, 508–518.

[4] a) Y. N. Zhao, J. A. Li, C. J. Li, K. Yin, D. Y. Ye, X. S. Jia, *Green Chem.* **2010**, *12*, 1370–1372; b) X. L. Feng, J. S. Wu, V. Enkelmann, K. Mullen, *Org. Lett.* **2006**, *8*, 1145–1148; c) S. S. Elmorsy, A. Pelter, K. Smith, *Tetrahedron Lett.* **1991**, *32*, 4175–4176.

[5] a) D. Y. K. Chen, R. H. Pouwer, J. A. Richard, *Chem. Soc. Rev.* **2012**, *41*, 4631–4642; b) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051–3060; c) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117–3179; d) H. Lebel, J. F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977–1050.

[6] a) S. Manna, A. P. Antonchick, *Org. Lett.* **2015**, *17*, 4300–4303; b) S. Manna, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2015**, *54*, 14845–14848; *Angew. Chem.* **2015**, *127*, 15058–15061.

[7] a) R. Samanta, R. Narayan, J. O. Bauer, C. Strohmann, S. Sievers, A. P. Antonchick, *Chem. Commun.* **2015**, *51*, 925–928; b) S. Manna, P. O. Serebrennikova, I. A. Utepova, A. P. Antonchick, O. N. Chupakhin, *Org. Lett.* **2015**, *17*, 4588–4591; c) R. Narayan, A. P. Antonchick, *Chem. Eur. J.* **2014**, *20*, 4568–4572; d) K. Matcha, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2014**, *53*, 11960–11964; *Angew. Chem.* **2014**, *126*, 12154–12158; e) S. Manna, K. Matcha, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2014**, *53*, 8163–8166; *Angew. Chem.* **2014**, *126*, 8302–8305; f) S. Manna, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2014**, *53*, 7324–7327; *Angew. Chem.* **2014**, *126*, 7452–7455; g) K. Matcha, R. Narayan, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2013**, *52*, 7985–7989; *Angew. Chem.* **2013**, *125*, 8143–8147; h) K. Matcha, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2013**, *52*, 2082–2086; *Angew. Chem.* **2013**, *125*, 2136–2140; i) A. P. Antonchick, L. Burgmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 3267–3271; *Angew. Chem.* **2013**, *125*, 3349–3353.

[8] a) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.* **2013**, *113*, 6234–6458; b) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed.* **2011**, *50*, 11062–11087; *Angew. Chem.* **2011**, *123*, 11256–11283; c) A. G. Csákÿ, J. Plumet, *Chem. Soc. Rev.* **2001**, *30*, 313–320.

[9] a) T. Piou, T. Rovis, *J. Am. Chem. Soc.* **2014**, *136*, 11292–11295; b) A. Saba, *J. Chem. Res. Synop.* **1990**, 288–289; c) J. J. Zhang, G. B. Schuster, *J. Am. Chem. Soc.* **1989**, *111*, 7149–7155; d) D. B. Reddy, V. M. Subramanyam, V. Padmavathi, *Org. Prep. Proced. Int.* **1988**, *20*, 83–86.

[10] K. Xu, Y. Fang, Z. C. Yan, Z. G. Zha, Z. Y. Wang, *Org. Lett.* **2013**, *15*, 2148–2151.

[11] H. Yi, Z. Liao, Z. G. Zhang, G. Zhang, C. Fan, X. Zhang, E. E. Bunel, C.-W. Pao, J.-F. Lee, A. Lei, *Chem. Eur. J.* **2015**, *21*, 18925–18929.

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