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Fluoride Anions in Self-Assembled Chiral Cage for the Enantioselective Protonation of Silyl Enol Ethers

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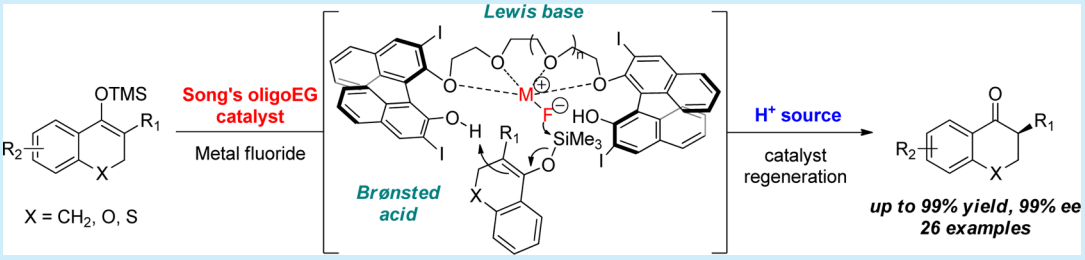
Supporting Information



ABSTRACT: The potential of Song's chiral oligoethylene glycols (oligoEGs) as catalysts was explored in the enantioselective protonation of trimethylsilyl enol ethers in combination with alkali metal fluoride (KF and CsF) and in the presence of a proton source. Highly enantioselective protonations of various silyl enol ethers of α-substituted tetralones were achieved, producing chiral α-substituted tetralones in full conversion and with up to 99% ee. The established protocol was successfully extended to the synthesis of biologically relevant chiral α-substituted chromanone and thiochromanone derivatives.

The proton is the smallest constituent in organic synthesis, and it is extremely challenging to control it in terms of enantioselectivity. Nevertheless, in nature, enzymes such as esterases and decarboxylases catalyze the enantioselective protonation of prochiral enolates for the construction of optically active α-tertiary carbonyl compounds.[1] Consequently, chiral α-carbonyl tertiary carbon stereocenters are common functionalities present in huge numbers of bioactive natural products. In contrast, the enantioselective introduction of protons into carbanions via synthetic routes is still challenging due to the small size of the proton. Furthermore, protonation reactions are among the most rapid, often diffusion-controlled reactions.[1,2]

During the past decade, several research groups have developed a number of strategies, especially catalytic methods, for the enantioselective protonation of enolate derivatives.[1−4] A significant number of organocatalytic methods[5] were developed for the asymmetric protonation of silyl enol ethers.[4] However, successful applications of chiral fluoride ions for enantioselective protonation reaction have been rare,[4a,c] possibly because of the high reactivity of such nascent fluoride ions, resulting in product racemization.[2a]

Recently, we reported easily accessible Song's chiral oligoEGs (Figure 1A), which bear phenols and polyether units, as organocatalysts for asymmetric cation-binding catalysis.[6,7] The ether oxygens act as a Lewis base to coordinate alkali metal fluorides, such as KF and CsF, thus generating a soluble fluoride anion in a confined chiral space. The terminal phenol groups are capable of simultaneously activating the electrophile via hydrogen bonding interaction, resulting in a well-organized transitions state leading to excellent stereoinduction in asymmetric catalysis.

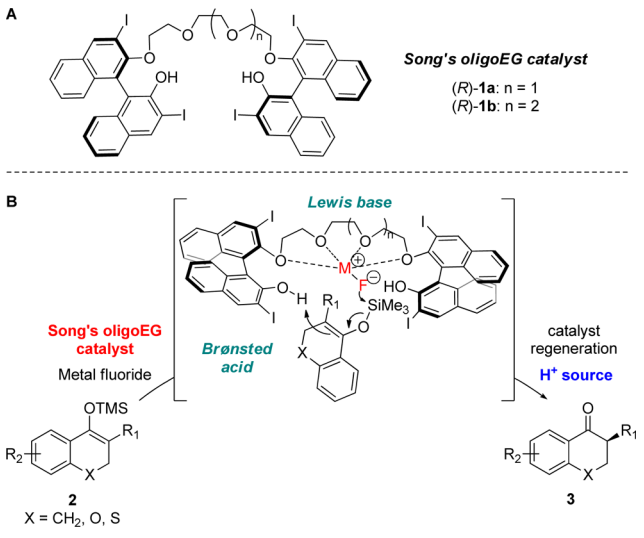


Figure 1. (A) Song's oligoEG catalysts. (B) Hypothesis for the mechanism of enantioselective protonation of silyl enol ethers catalyzed by Song's chiral oligoEGs.

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We envisioned that our cation-binding catalyst system would be ideally suited for the enantioselective protonation reaction of silyl enol ethers **2**. As shown in Figure 1B, the soluble chiral fluoride anion was generated in situ upon the activation of MF by the chiral cation-binding catalyst. Subsequently, it can promote desilylation of silyl enol ethers, producing the enol intermediate, which can then be protonated enantiomerically by the phenolic proton of the catalyst, affording the desired enantio-enriched α-substituted ketone product. The metal salt of the catalyst can then be regenerated by means of an additional proton source. The chiral cage, in situ formed by the incorporation of alkali metal fluoride salt, creates an ideal active site architecture, in which the reactive fluoride and the silyl enol ether can be brought into proximity, consequently enhancing the reactivity as well as efficiently transferring the stereochemical information (Figure 1B).

Here, we report highly enantioselective organocatalytic protonation of trimethylsilyl enol ethers of cyclic ketones using cesium fluoride and Song's chiral oligoEGs as a cation-binding catalyst in the presence of a suitable proton source.

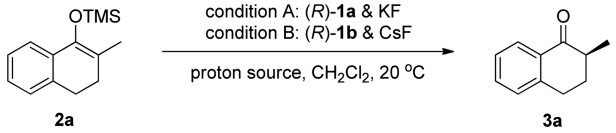
In general, enantioselective protonation is a kinetically controlled process, which requires a balance of acidity between the chiral protonating catalyst, the stoichiometric proton source, and the substrate.[2a] This must be achieved in order to obtain an optimized rate of protonation through the catalyzed pathway by avoiding undesired background reactions. The desired protonation is required to be as complete as possible, as otherwise nonselective protonation reactions will occur during workup. With this in mind, we have conducted a systematic study by carefully choosing catalysts as well as proton sources in order to find optimal conditions for the enantioselective protonation reaction of silyl enol ether **2a** as the model substrate. The catalytic results are summarized in Table 1.

As shown in Table 1, the ether chain length is critical for the catalytic performance in this reaction (entries 1−5 vs entries 6−13). Although the catalyst (*R*)-**1a** in combination with KF showed promising enantioselectivity (up to 94% ee), the observed activity was unsatisfactory, regardless of the type of proton source (9−75% conversion even after 100 h) (entries 1−5). These observed slow reaction rates can be attributed to the low concentration of soluble fluoride anion in the reaction mixture. However, to our delight, the same reaction using (*R*)-**1b** in combination with more soluble cesium fluoride proceeded much faster (>99% conversion) than those observed with **1a** and KF (entries 6−13). In particular, when using 4-nitrocatechol or (*R*)-3,3′-diiodo-BINOL as the proton source (see Supporting Information for more detailed proton source screening), almost full conversion even at 0 °C and quantitative enantioselectivity were observed. These results indicate that the proper combination of chiral cage size, fluoride source, and proton source is critical for effective catalytic performance. In further experiments performed with (*R*)-**1b** as the optimal catalyst and 4-nitrocatechol as the proton source, different solvents were examined (see Supporting Information for solvent screening).

However, all tested solvents, nonpolar and polar, led to lower yields and asymmetric induction (see Supporting Information). In summary, the combination of catalyst **1b**, CsF as fluoride source, (*R*)-3,3′-diiodo-BINOL as proton donor, and CH_2Cl_2 as solvent provided the best result.

To further support our hypothesized reaction mechanism, we performed the reaction of **2a** with CsF using a stoichiometric amount of catalyst (*R*)-**1b** in the absence of an additional proton source, where catalyst regeneration is not required (entry 13, Table 1). As expected, full conversion of **2a** (>99%) was observed within 12 h, affording **3a** with 99% ee.

Table 1. Optimization of Reaction Conditions[a]



2a **3a**

entry	condition	proton source	time (h)	conversion (%)[b]	ee (%)[c]
1	A	catechol	48	75	84
2	A	4-nitro-catechol	100	39	70
3	A	Amberlite CG 50	100	65	91
4	A	*rac*-BINOL	72	55	94
5	A	(*S*)-3,3′-I_2-BINOL	72	9	93
6	B	catechol	72	92	90
7	B	4-nitro-catechol	24	>99	90
8[d]	B	4-nitro-catechol	96	99	96
9	B	Amberlite CG 50	96	92	92
10	B	(*S*)-3,3′-I_2-BINOL	48	80	94
11	B	(*R*)-3,3′-I_2-BINOL	48	>99	94
12[d]	B	(*R*)-3,3′-I_2-BINOL	48	99	99
13[d,e]	B	no proton source	12	>99	99

[a]Condition A: **2a** (0.05 mmol), (*R*)-**1a** (10 mol %), KF (0.1 mmol), and the proton source (0.06 mmol) in CH_2Cl_2 (0.05 M) at 20 °C. Condition B: **2a** (0.05 mmol), (*R*)-**1b** (10 mol %), CsF (0.1 mmol), and the proton source (0.06 mmol) in CH_2Cl_2 (0.05 M) at 20 °C. [b]Conversion was determined by ^{1}H NMR analysis of the unpurified reaction mixture. [c]Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. [d]Reaction was performed at 0 °C. [e]Using 100 mol % (*R*)-**1b**. (*S*)/(*R*)-3,3′-I_2-BINOL: (*S*)/(*R*)-3,3′-diiodo-1,1′-bi-2-naphthol.

Having optimized the reaction conditions (entry 12, Table 1), we then examined the generality of the reaction by subjecting various silyl enol ethers (**2a**−**2p**) derived from cyclic ketones, which are summarized in Scheme 1. Silyl enol ethers of tetralones (**2a**−**2l**) with different substituted alkyl and benzyl chains were smoothly protonated to the corresponding chiral α-substituted tetralones (**3a**−**3l**) in high chemical yields and excellent enantioselectivities (up to 99% yield and 99% ee).[8] Using commercially available 4-nitrocatechol as a proton source, similar conversions were obtained, albeit with slightly lower enantioselectivity (**3a**, **3d**, and **3i**). To our delight, the present reaction conditions for the enantioselective protonation are also applicable to the synthesis of chiral α-substituted chromanone and thiochromanone derivatives **3m**−**3p**, which constitute the basic structure of natural products[9] possessing diverse biological activities such as antimutagenic[10] and anti-inflammatory[11] properties. The palladium-catalyzed enantioselective decarboxylative protonation was also applied to the synthesis of 3-substituted 4-chromanones by Muzart and co-workers. However, very low enantioselectivities were obtained (22−60% ee).[12]

This method was also suitable for the synthesis of chiral α-allyl and ethyl acetate substituted tetralones, chromanones, and thiochromanone derivatives **2q**−**2z** with excellent yields and enantioselectivities (up to 99% yield and 97% ee, Scheme 2). Chiral α-allyl and ethyl acetate substituted tetralones, chromanones, and thiochromanone derivatives were previously

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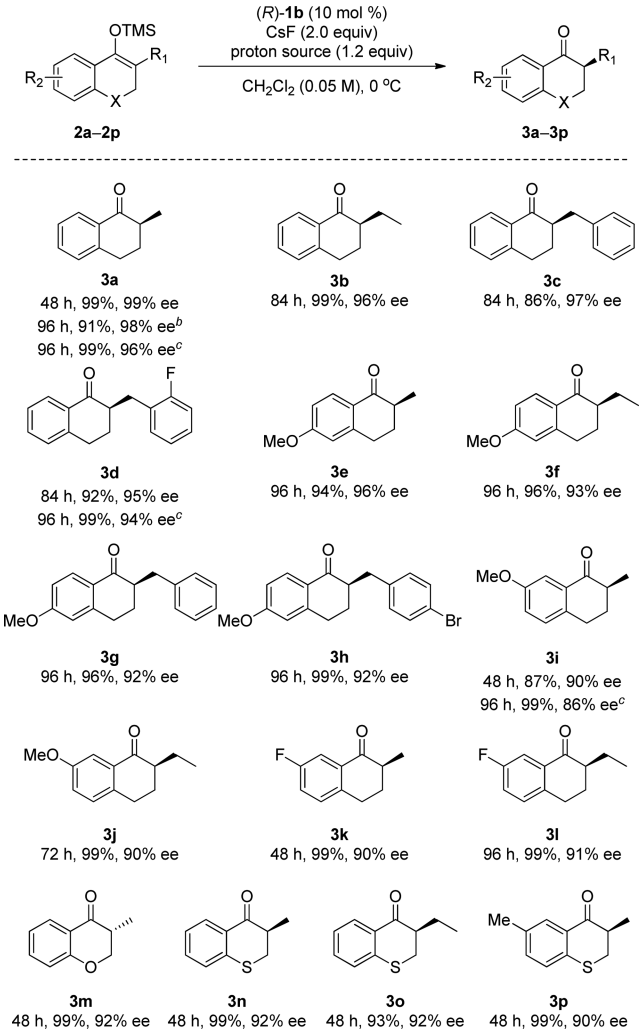
Scheme 1. Enantioselective Protonation of Trimethylsilyl Enol Ethers of α-Alkyl Substituted Tetralones, Chromanone, and Thiochromanones[a]

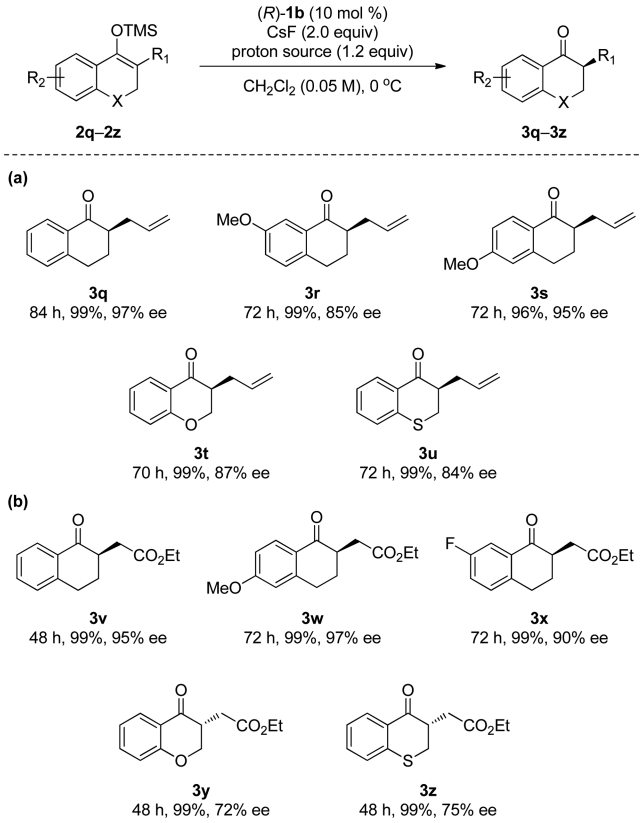


[a]Unless otherwise indicated, the reactions were performed with **2** (0.05 mmol), (*R*)-**1b** (10 mol %), CsF (0.1 mmol), and (*R*)-3,3′-diiodo BINOL (0.06 mmol) as proton source in CH_2Cl_2 (0.05 M) at 0 °C. [b]The reaction was carried out on 1 mmol scale. [c]Using 4-nitrocatechol (0.06 mmol) as the proton source.

prepared by a palladium catalyzed decarboxylative asymmetric allylic alkylation reaction[13] and *N*-heterocyclic carbene-catalyzed enantioselective intramolecular Stetter reaction,[14] respectively.

In summary, we developed a method for the highly enantioselective protonation of trimethylsilyl enol ethers of cyclic ketones by using a highly accessible Song's chiral oligoethylene glycol (oligoEG) as the cation binding catalyst and CsF as the base in the presence of a proton source. Excellent enantioselectivities were obtained with a variety of α-substituted tetralones. This protocol was also successfully extended to the synthesis of biologically relevant chiral α-substituted chromanone and thiochromanone derivatives. The salient features of this process include (a) a transition-metal-free and operationally simple procedure, (b) a broad substrate scope, and (c) excellent enantioselectivity with up to 99% ee. The extension of this strategy to an extremely challenging α-

Scheme 2. Enantioselective Synthesis of α-Allyl and α-Ethyl acetate Tetralones, Chromanones, and Thiochromanones by Organocatalytic Enantioselective Protonation[a]



[a]Unless otherwise indicated, the reactions were performed with **2** (0.05 mmol), (*R*)-**1b** (10 mol %), CsF (0.1 mmol), and (*R*)-3,3′-diiodo BINOL (0.06 mmol) as proton source in CH_2Cl_2 (0.05 M) at 0 °C.

substituted acyclic ketone system is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01429.

Experimental details, analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1*, 359.

(2) (a) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566. (b) Yanagisawa, A.; Ishihara, K.; Yamamoto, H. *Synlett* **1997**, *1997*, 411. (c) Eames, J.; Weerasooriya, N. *Tetrahedron: Asymmetry* **2001**, *12*, 1. (d) Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653. (e) Claraz, A.; Oudeyer, S.; Levacher, V. *Curr. Org. Chem.* **2012**, *16*, 2192. (f) Oudeyer, S.; Brière, J.-F.; Levacher, V. *Eur. J. Org. Chem.* **2014**, *2014*, 6103. (g) Legros, F.; Oudeyer, S.; Levacher, V. *Chem. Rec.* **2017**, *17*, 429.

(3) (a) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (b) Yanagisawa, A.; Kikuchi, T.; Kuribayashi, T.; Yamamoto, H. *Tetrahedron* **1998**, *54*, 10253. (c) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120. (d) Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 24. (e) Yanagisawa, A.; Touge, T.; Arai, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1546. (f) Mitsuhashi, K.; Ito, R.; Arai, T.; Yanagisawa, A. *Org. Lett.* **2006**, *8*, 1721. (g) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246. (h) Morita, M.; Drouin, L.; Motoki, R.; Kimura, Y.; Fujimori, I.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3858. (i) Uraguchi, D.; Kinoshita, N.; Ooi, T. *J. Am. Chem. Soc.* **2010**, *132*, 12240. (j) Cheon, C. H.; Imahori, T.; Yamamoto, H. *Chem. Commun.* **2010**, *46*, 6980. (k) Cheon, C. H.; Kanno, O.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 13248. (l) Yanagisawa, A.; Sugita, T.; Yoshida, K. *Chem. - Eur. J.* **2013**, *19*, 16200.

(4) (a) Poisson, T.; Dalla, V.; Marsais, F.; Dupas, G.; Oudeyer, S.; Levacher, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7090. (b) Poisson, T.; Oudeyer, S.; Dalla, V.; Marsais, F.; Levacher, V. *Synlett* **2008**, *2008*, 2447. (c) Poisson, T.; Gembus, V.; Dalla, V.; Oudeyer, S.; Levacher, V. *J. Org. Chem.* **2010**, *75*, 7704. (d) Claraz, A.; Leroy, J.; Oudeyer, S.; Levacher, V. *J. Org. Chem.* **2011**, *76*, 6457. (e) Beck, E. M.; Hyde, A. M.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 4260. (f) Yamamoto, E.; Gokuden, D.; Nagai, A.; Kamachi, T.; Yoshizawa, K.; Hamasaki, A.; Ishida, T.; Tokunaga, M. *Org. Lett.* **2012**, *14*, 6178. (g) Claraz, A.; Landelle, G.; Oudeyer, S.; Levacher, V. *Eur. J. Org. Chem.* **2013**, *2013*, 7693. (h) Guin, J.; Varseev, G.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 2100.

(5) (a) Dalko, P. I.; Moisan, L. *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis, Supplement 2*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 2004; p 125. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.

(6) Oliveira, M. T.; Lee, J.- W. *ChemCatChem* **2017**, *9*, 377 and references therein.

(7) (a) Yan, H.; Jang, H. B.; Lee, J. W.; Kim, H. K.; Lee, S. W.; Yang, J.; Song, C. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 8915. (b) Yan, H.; Oh, J. S.; Lee, J. W.; Song, C. E. *Nat. Commun.* **2012**, *3*, 1212. (c) Park, S. Y.; Lee, J. W.; Song, C. E. *Nat. Commun.* **2015**, *6*, 7512. (d) Li, L.; Liu, Y.; Peng, Y.; Yu, L.; Wu, X.; Yan, H. *Angew. Chem., Int. Ed.* **2016**, *55*, 331. (e) Liu, Y.; Ao, J.; Paladhi, S.; Song, C. E.; Yan, H. *J. Am. Chem. Soc.* **2016**, *138*, 16486. (f) Vaithiyanathan, V.; Kim, M. J.; Liu, Y.; Yan, H.; Song, C. E. *Chem. - Eur. J.* **2017**, *23*, 1268. (g) Kim, M. J.; Xue, L.; Liu, Y.; Paladhi, S.; Park, S. J.; Yan, H.; Song, C. E. *Adv. Synth. Catal.* **2017**, *359*, 811. (h) Yu, L.; Wu, X.; Kim, M. J.; Vaithiyanathan, V.; Liu, Y.; Tan, Y.; Qin, W.; Song, C. E.; Yan, H. *Adv. Synth. Catal.* **2017**, DOI: 10.1002/adsc.201700015. (i) Park, S. Y.; Hwang, I. S.; Lee, H. J.; Song, C. E. *Nat. Commun.* **2017**, *8*, 14877. (j) Tan, Y.; Luo, S.; Li, D.; Zhang, N.; Jia, S.; Liu, Y.; Qin, W.; Song, C. E.; Yan, H. *J. Am. Chem. Soc.* **2017**, *139*, 6431. (k) Duan, M.; Liu, Y.; Ao, J.; Xue, L.; Luo, S.; Tan, Y.; Qin, W.; Song, C. E.; Yan, H. *Org. Lett.* **2017**, *19*, 2298.

(8) We also examined other types of α-substituted cyclic ketones (e.g., 2-methylindanone, 2-methylbenzocycloheptan-1-one, 2-benzyl-1-cyclohexanone, and 1-methyl-2-tetralone) as well as acyclic ketones (e.g., 2-methylbutyrophenone and 2-methyl-1,3-diphenylpropan-1-one). However, unfortunately, only low to moderate enantioselectivities were obtained. For details, see Supporting Information.

(9) (a) Adinolfi, M.; Aquila, T.; Barone, G.; Lanzetta, R.; Parrilli, M. *Phytochemistry* **1989**, *28*, 3244. (b) Corsaro, M. M.; Lanzetta, R.; Mancino, A.; Parrilli, M. *Phytochemistry* **1992**, *31*, 1395.

(10) Wall, M. E.; Wani, M. C.; Manikumar, G.; Taylor, H.; McGivney, R. *J. Nat. Prod.* **1989**, *52*, 774.

(11) Loggia, R.; Del Negro, P.; Tubaro, A.; Barone, G.; Parrilli, M. *Planta Med.* **1989**, *55*, 587.

(12) Roy, O.; Loiseau, F.; Riahi, A.; Hénin, F.; Muzart, J. *Tetrahedron* **2003**, *59*, 9641.

(13) (a) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846. (b) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343.

(14) For selected examples on an enantioselective intramolecular Stetter reaction using chiral triazolium salts, see: (a) Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (b) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (c) de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284. (d) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195. (e) de Alaniz, J. R.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 2033. (f) Moore, J. L.; Silvestri, A. P.; de Alaniz, J. R.; DiRocco, D. A.; Rovis, T. *Org. Lett.* **2011**, *13*, 1742. (g) Rafiński, Z.; Kozakiewicz, A.; Rafińska, K. *ACS Catal.* **2014**, *4*, 1404.

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