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Chiral Bicylic Guanidine-Catalyzed Conjugate Addition of α-Fluoro-β-Ketoesters to Cyclic Enones

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Abstract:

By utilizing a chiral bicyclic guanidine as catalyst and triethylamine as additive, the first asymmetric Michael addition of α-fluoro-β-ketoesters to various cyclic enones has been successfully developed, affording a variety of Michael adducts with potential synthetic utilities with satisfactory stereoselectivity (up to 94% ee and 4.3:1 dr).

Keywords: asymmetric synthesis; organocatalysis; guanidine; cyclic enones; α-fluoro-β-ketoesters

Exchange of hydrogen with a fluorine atom in biologically active compounds, namely monofluorination, has received increasing interest particularly in pharmaceutical research, since the monofluorinated analogues as bioisosteres of parent molecules often enhance desirable properties and do not require significant modifications in the molecular structures.[1] The development of an efficient method for the specific incorporation of fluorine in a stereoselective manner has thus attracted considerable

attention in organic and medicinal chemistry in the past few decades.[2] The stereoselective introduction[2] of a fluorine atom into a challenging quaternary stereogenic center[3] of chiral compound has been demonstrated as one of the most efficient protocols to obtain the chiral monofluorinated compounds.

In 2008, Maruoka and co-workers presented an original application of α-fluoro-β-ketoesters as fluorocarbon nucleophiles in asymmetric amination with moderate enantioselectivity.[4] Later in 2009, Lu and co-workers introduced a highly enantioselective Michael addition of α-fluoro-β-ketoesters to nitroalkenes with moderate diastereoselectivity.[5] Almost simultaneously, we reported the asymmetric Michael additions of α-fluoro-β-ketoesters with *N*-maleimides and *trans*-4-oxo-4-arylbutenamides in excellent enantio- and diastereoselectivity.[6] Since then, α-fluoro-β-ketoesters or their analogues have been successively applied in a series of asymmetric reactions, such as Robinson annulation,[7] amination,[8] Mannich reaction,[9] allylic alkyation with Morita-Baylis-Hillman carbonates[10]. However, cyclic enones, which have been utilized as electrophiles in many asymmetric reactions to access various chiral compounds with important biological activities,[11] has never been attempted to react with α-fluoro-β-ketoesters, probably due to their formidable poor reactivity as electrophile.[11d-e]

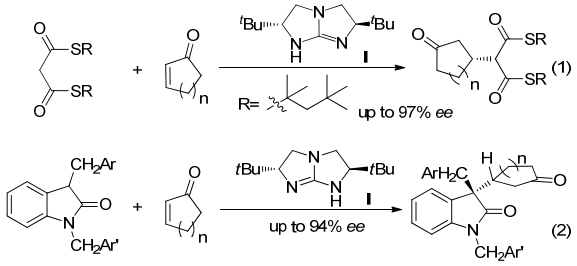


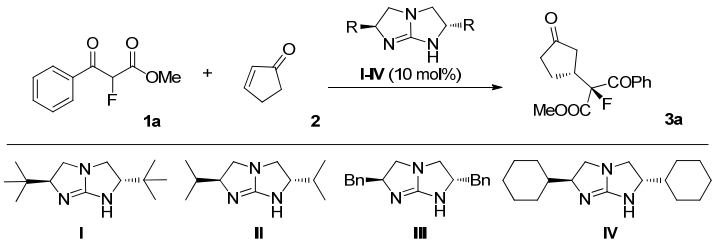
Figure 1. Our preliminary works for investigating Michael addition reactions by using cyclic ketones as electrophiles

In 2007, we[11d] introduced highly enantioselective Michael reactions of dithiomalonates with cylic enones, in which the chiral bicylic guanidine[12] **I** was demonstrated to be an efficient catalyst for its high p*K*a value (Figure 1, eqn. 1). The catalytic ability of the guanidine **I** to cyclic enones was verified once more when 3-benzyl oxindoles were used as nucleophiles.[11n] Indeed, the chiral bicyclic-guanidines have exhibited their strong catalytic and stereoselective activities in many asymmetric reactions, including the Dies-Alder reaction,[13a] protonation,[13b-d] the Mannich reaction,[9b] decarboxylative reaction,[13e] the Michael reaction,[6,11d-e,11n,13f-h] vinylogous amination,[13i] amination[13j] and alkylation[13k]. Therefore, we envisioned that the Michael addition of α-fluoro-β-ketoesters to cyclic enones could be addressed by utilizing this kind of well-established guanidines as catalyst.

As our initial study, the Michael addition of α-fluoro-β-ketoester **1a** to 2-cyclopentenone **2** was selected as the model reaction to investigate the reaction conditions (Table 1). It was found that the reaction worked smoothly at 25 ^{o}C in toluene as solvent when in the presence of 10 mol% of guanidine **I** as catalyst, affording the desired adduct **3a** in 92% yield with 75% ee and 2:1 dr (Table 1, entry 1). The satisfactory results prompted us to evaluate other guanidines **II**-**IV** with different side chains (Table 1, entries 2–4). However, no better results were obtained and guanidine **I** was proved as the best catalyst. Subsequently, the solvent effect was

evaluated in the process (Table 1, entries 5–10). THF as solvent could improve the ee value to 87% with the same diastereoselectivity (Table 1, entry 6). To our surprise, no reaction was detected when diethyl ether and ethyl acetate were utilized as solvent (Table 1, entries 7–8). Following a decrease in temperature to 10 ^{o}C, no improvement of stereoselectivity was achieved when THF was solvent (Table 1, entry 10), but toluene could give the better results (90% ee, 3:1 dr, Table 1, entry 11). The reaction in toluene at −10 ^{o}C was thus conducted, and the adduct **3a** was obtained in 40% yield with 93% ee and 3:1 dr after 22 hours (Table 1, entry 13). In our previous work,[11e] we have demonstrated that Et_3N could accelerate the reaction rate and without compromising ee values in guanidine **I**-catalyzed Michael reactions. Therefore, 0.1 equiv of Et_3N was used as additive under the same reaction conditions. We were delighted that the reaction was finished within 45 hours to afford the adduct **3a** in 93% yield with 92% ee and 3:1 dr (Table 1, entry 14). Although the similar improved results were obtained when using pyridine or *i*Pr_2EtN as additive (Table 1, entries 15–16), Et_3N was considered as the best additive for its low boiling point and convenient removal.

Table 1. Screening studies on reaction conditions.



Entry	Catalyst	Solvent	*T* (^{o}C)	*t* (h)	Yield^{A} [%]	Ee^{B} [%]	Dr^{C}
1	**I**	Toluene	25	44	92	75	2:1

2	**II**	Toluene	25	27	94	73	2:1
3	**III**	Toluene	25	25	86	33	2:1
4	**IV**	Toluene	25	25	93	67	3:1
5	**I**	CH_2Cl_2	25	44	55	0	1:1
6	**I**	THF	25	44	96	87	2:1
7	**I**	Et_2O	25	44	Trace	N.A.	N.A.
8	**I**	EtOAc	25	44	Trace	N.A.	N.A.
9	**I**	CH_3CN	25	44	64	7	1:1
10	**I**	THF	10	23	83	89	2:1
11	**I**	Toluene	10	22	83	90	3:1
12	**I**	Toluene	0	22	47	91	3:1
13	**I**	Toluene	–10	22	40	93	3:1
14[D]	**I**	Toluene	–10	45	93	92	3:1
15[E]	**I**	Toluene	–10	45	93	91	3:1
16[F]	**I**	Toluene	–10	45	91	92	3:1

[A]Yield of isolated product.

[B]Determined by HPLC method.

[C]Determined by ^{1}H NMR analysis of the crude material.

[D]Et_3N (0.1 equiv) was used.

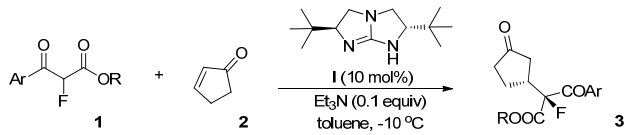
[E]Pyridine (0.1 equiv) was used.

[F]*i*Pr_2EtN (0.1 equiv) was used.

Subsequently, we began to investigate the versatility of this protocol by examining the Michael reactions of various α-fluoro-β-ketoesters **1** with 2-cyclopentenone **2** under the optimal reaction conditions (10 mol% of guanidine **I**, 0.1 equiv of Et_3N in toluene at –10 ^oC). The results are summarized in Table 2. The corresponding adducts were obtained in 74–95% yield with 81–94% ee and a dr of 1.5:1 to 4.3:1. It was found that α-fluoro-β-ketoester **2b**, containing ethyl as a bulkier ester group, could afford the corresponding adduct **3b** with similar enantio- and diastereoselectivity (90% ee, 3:1 dr, Table 1, entry 1). The α-fluoro-β-ketoesters (**1c-f**) with electron-withdrawing groups on *para*- and *meta*-positions of their phenyl rings (Table

2, entries 2–5) should gave higher enantioselectivities than those (**1g-i**) with electron-withdrawing groups in the *ortho*-position (Table 2, entries 6–8). A similar trend regarding enantioselectivity was found with α-fluoro-β-ketoesters (**1j-o**) with the electron-neutral and donating groups on their phenyl rings (Table 2, entries 9–14). Moreover, excellent ee value could be obtained when the phenyl ring of α-fluoro-β-ketoester was replaced with hetereoaromatic group, such as furyl (Table 2, entry 15). To evaluate the versatility of this protocol, other cyclic ketones, such as 2(5*H*)-furanone **4** and 2-cyclopentenone **6** were attempted in succession (Scheme 1). 2(5*H*)-furanone **4** exhibited lower reactivity than 2-cyclopentenone **2**; the adduct **5** was obtained in 43% yield with 82% ee and 2.3:1 dr after 72 hours (Eq. 1). Good yield with good enantioselectivity and moderate diastereoselectivity was achieved when using 2-cyclopentenone **6** as electrophile (Eq. 2).

Table 2. Michael addition of various α-fluoro-β-ketoesters **1** to 2-cyclopentenone **2** catalyzed by bicyclic guanidine **I**.



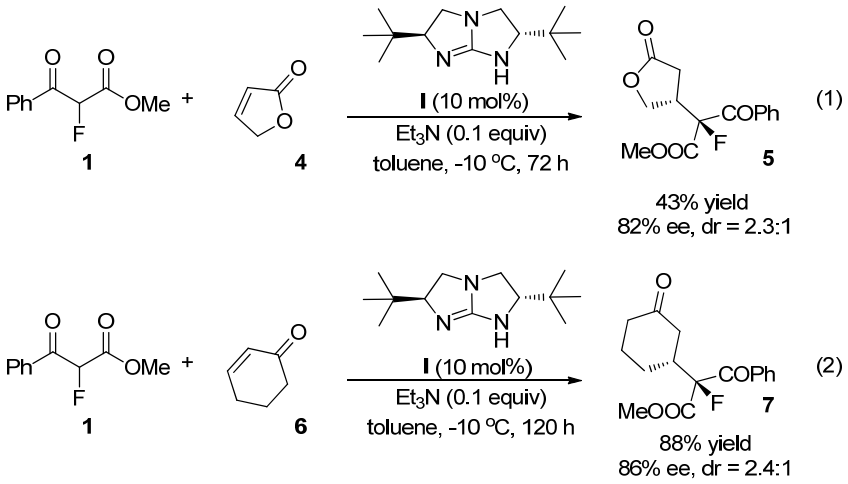
Entry	**1** (Ar, R)	*t* (h)	**3**	Yield[A] [%]	Ee[B] [%]	Dr[C]
1[D]	**1b** (Ph, Et)	71	**3b**	92	90	3.0:1
2	**1c** (4-FPh, Me)	68	**3c**	90	93	3.6:1
3	**1d** (4-ClPh, Me)	69	**3d**	90	93	3.5:1
4	**1e** (4-BrPh, Me)	51	**3e**	77	91	3.8:1
5	**1f** (3-BrPh, Me)	70	**3f**	79	91	2.9:1
6	**1g** (2-FPh, Me)	54	**3g**	84	85	1.5:1
7	**1h** (2-ClPh, Me)	48	**3h**	91	82	1.6:1
8	**1i** (2-BrPh, Me)	63	**3i**	74	81	1.5:1
9	**1j** (4-MePh, Me)	69	**3j**	87	93	3.6:1
10	**1k** (4-MeOPh, Me)	70	**3k**	91	93	3.6:1
11	**1l** [4-(4-BrPh)Ph, Me]	47	**3l**	64	94	4.3:1
12	**1m** (2-MePh, Me)	69	**3m**	93	87	3.0:1
13	**1n** (2-MeOPh, Me)	72	**3n**	92	84	1.8:1
14	**1o** (3-MeOPh, Me)	74	**3o**	95	92	3.7:1
15	**1p** (2-furyl, Me)	72	**3p**	92	90	2.8:1

[A]Yield of isolated product.

[B]Determined by HPLC method.

[C]Determined by ^{1}H NMR analysis of the crude material.

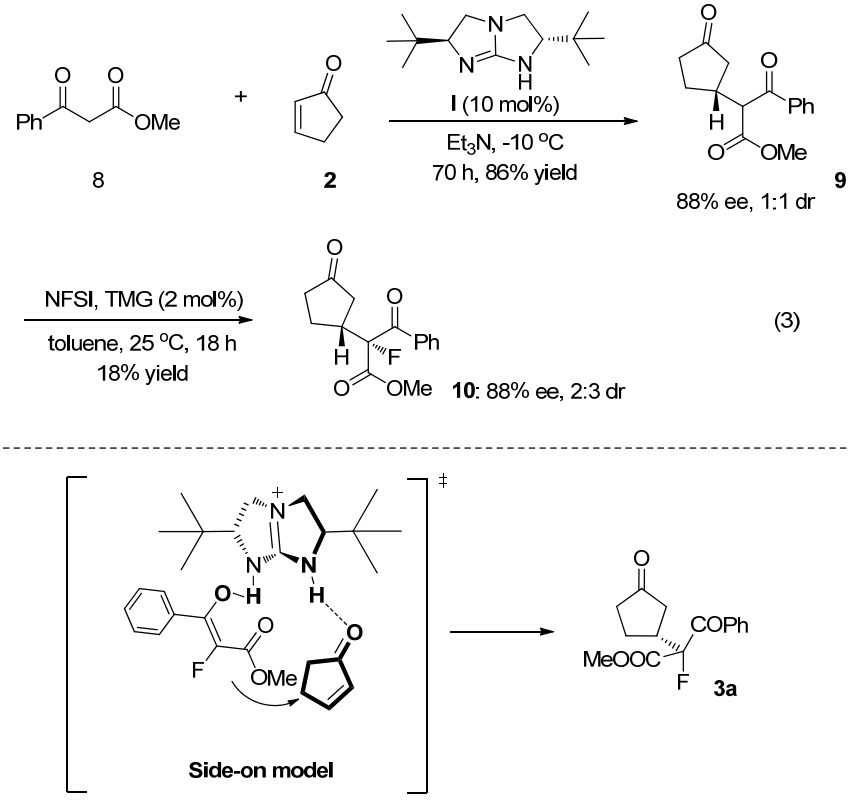
[D]5.0 mmol scale, 80 hours, 86% yield, 90% ee and 3:1 dr.



Scheme 1. Bicyclic-guanidine-catalyzed Michael addition of α-fluoro-β-ketoester **1a** to 2(5*H*)-furanone **4** (Eq. 1); Michael addition of α-fluoro-β-ketoester **1a** to 2-cyclohexenone **6** (Eq. 2)

Indeed, we have attempted to synthesize these monofluorinated compounds from β-ketoester **8**. As Scheme 2 shown, the reaction between β-ketoester **8** and 2-cyclopentenone **2** was conducted in the presence of 10 mol% of guanidine **I** at −10 °C in triethylamine as solvent. As we anticipated,[11e] the reaction could be finished after 70 hours, affording adduct **9** in 86% yield with 88% ee and 1:1 dr. However, the fluorination of **9** using *N*-fluorobenzenesulfonimide (NFSI) as fluorine source and 1,1,3,3-tetramethyl guanidine (TMG) as catalyst at 25 °C was very slow, and only

18% yield of the product **10** was obtained. The HPLC analysis indicated that the compound **10** was a diastereomer of **3a** with the same enantiomeric identity (see the Supporting Information for details). Combining these results with the currently understood mechanism of guanidine **I**,[6] a transition state with a side-on manner was proposed and the absolute configuration of these monofluorinated adducts was reasonably assigned. Although the role of Et_3N in the reaction is not clear, the changed medium by Et_3N decreasing the activation energy is a plausible mechanism.



Scheme 2. The preparation of monofluorinated adduct **10** from a Michael addition-fluorination reaction and proposed transition-state model.

In conclusion, we have developed the first asymmetric Michael additions of

α-fluoro-β-ketoesters to various cyclic enones. A bicyclic guanidine was verified as an efficient chiral catalyst for the reactions. The direct protocol provides a readily method to construct a monofluorinated quaternary chiral center on cyclic ketones with high stereoselectivity. Other reactions utilizing α-fluoro-β-ketoesters as nucleophiles to access a variety of monofluorinated compounds are in progress and will be reported in due course.

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REFERENCES

[1] (a) Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications (Eds.: R. Filler, Y. Kobayashi, L. M. Yagupolskii), Elsevier, **1993**. (b) T. Hiyama, in Organofluorine Compounds: Chemistry and Applications, Springer, Berlin, **2000**. (c) K. Uneyama in Organo-fluorine Chemistry, Blackwell, Oxford, **2006**. (d) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308. (e) T. Furuya, A. S. Kamlet, T. Ritter, *Nature*, **201**1, *473*, 470.

[2] For selected reviews, see: (a) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119. (b) H. Ibrahim, A. Togni, *Chem. Commun.* **2004**, 1147. (c) P. M. Pihko, *Angew. Chem. Int. Ed.* **2006**, *45*, 544. (d) V. A. Brunet, D. O'Hagan, *Angew. Chem. Int. Ed.* **2008**, *47*, 1179. (e) S. Lectard, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.* **2010**, *352*, 2708. (f) D. Cahard, X. Xu, S. Couve-Bonnaire, X. Pannecoucke, *Chem. Soc. Rev.* **2010**, *39*, 558. (g) C. Hollingworth, V. Gouverneur, *Chem. Commun.* **2012**, *48*, 2929.

[3] (a) J. Christoffers, A. Mann, *Angew. Chem. Int. Ed.* **2001**, *40*, 4591. For a recent book, see: (b) *Quaternary Stereocenters* (Eds: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**.

[4] R. He, X. Wang, T. Hashimoto, K. Maruoka, *Angew. Chem. Int. Ed.* **2008**, *47*, 9466.

[5] X. Han, J. Luo, C. Liu, Y. Lu, *Chem. Commun.* **2009**, 2044.

[6] Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K.-W. Huang, M. W. Wong, C.-H. Tan, *Angew. Chem. Int. Ed.* **2009**, *48*, 3627.

[7] H.-F. Cui, Y.-Q. Yang, Z. Chai, P. Li, C.-W. Zheng, S.-Z. Zhu, G. Zhao, *J. Org. Chem.* **2010**, *75*, 117.

[8] X. Han, F. Zhong, Y. Lu, *Adv. Synth. Catal.* **2010**, *352*, 2778.

[9] (a) X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem. Int. Ed.* **2009**, *48*, 7604. (b) Y. Pan, Y. Zhao, T. Ma, Y. Yang, H. Liu, Z. Jiang, C.-H. Tan, *Chem. Eur. J.* **2010**, *16*, 779. (c) Y. Kang, D. Y. Kim, *Tetrahedron Lett.* **2011**, *52*, 2356. (d) S. J. Yoon, Y. K. Kang, D. Y. Kim. *Synlett* **2011**, 420.

[10] L. Yan, Z. Han, B. Zhu, C. Yang, C.-H. Tan, Z. Jiang, *Beilstein J. Org. Chem.* **2013**, *9*, 1853.

[11] (a) A. Prieto, N. Halland, K. A. Jørgensen, *Org. Lett.* **2005**, *7*, 3897. (b) M. Shi, W. Zhang, *Adv. Synth. Catal.* **2005**, *347*, 535. (c) S. Hanessian, Z. Shao, J. S. Warrier, *Org. Lett.* **2006**, *8*, 4787. (d) W. Ye, Z. Jiang, Y. Zhao, S. L. M. Goh, D. Leow, Y.-T. Soh, C.-H. Tan, *Adv. Synth. Catal.* **2007**, *349*, 2454. (e) Z. Jiang, W. Ye, Y. Yang, C.-H. Tan, *Adv. Synth. Catal.* **2008**, *350*, 2345. (f) K. Kawamura, H. Fukuzawa, M. Hayashi, *Org. Lett.* **2008**, *10*, 3509. (g) Y. Tanaka, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 6072. (h) P. Li, Y. Wang, X. Liang, J. Ye, *Chem. Commun.* **2008**, 3302. (i) A. J. Smith, L. K. Abbott, S. F. Martin, *Org. Lett.* **2009**, *11*, 4200. (j) F. Pesciaioli, X. Tian, G. Bencivenni, G. Bartoli, P. Melchiorre, *Synlett* **2010**, 1704. (k) M. H. Freund, S. B. Tsogoeva, *Synlett* **2011**, 503. (l) J. Streuff, *Chem. Eur. J.* **2011**, *17*, 5507. (m) N. Shibata, M. Yoshimura, H. Yamada, R. Arakawa, S. Sakaguchi, *J. Org. Chem.* **2012**, *77*, 4079. (n) C. Yang, W. Chen. W. Yang, B. Zhu, L. Yan, C.-H. Tan, Z. Jiang, *Chem. Asian J.* **2013**, *8*, 2960.

[12] For selected reviews, see: (a) D. Leow, C.-H. Tan, *Chem. Asian J.* **2009**, *4*, 488. (b) M. P. Coles, *Chem. Commun.* **2009**, 3659. (c) D. Leow, C.-H. Tan, *Synlett* **2010**, 1589. (d) X. Fu, C.-H. Tan, *Chem. Commun.* **2011**, *47*, 8210. (e) P. Selig, *Synthesis*, **2013**, *45*, 703. For selected examples, see: (f) E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157. g) M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454. (h) M. Terada, M. Nakano, H. Ube, *J. Am. Chem. Soc.* **2006**, *128*, 16044. (i) M. Terada, T. Ikehara, H. Ube, *J. Am. Chem.*

Soc. **2007**, *129*, 14112. (j) H. Ube, N. Shimada, M. Terada, *Angew. Chem. Int. Ed.* **2010**, *49*, 1858. (k) M. Terada, K. Ando, *Org. Lett.* **2011**, *13*, 2026. (l) S. Dong, X. Liu, Y. Zhang, L. Lin, X. Feng, *Org. Lett.* **2011**, *13*, 5060. (m) X. Xiao, X. Liu, S. Dong, Y. Cai, L. Lin, X. Feng, *Chem. Eur. J.* **2012**, *18*, 15922.

[13] (a) J. Shen, T. T. Nguyen, Y.-P. Goh, W. Ye, X. Fu, J. Xu, C.-H. Tan, *J. Am. Chem. Soc.* **2006**, *128*, 13692. (b) D. Leow, S. Lin, S. K. Chittimalla, X. Fu, C.-H. Tan, *Angew. Chem. Int. Ed.* **2008**, *47*, 5641. (c) H. Liu, D. Leow, K.-W. Huang, C.-H. Tan, *J. Am. Chem. Soc.* **2009**, *131*, 7212. (d) Y. Zhao, X. Lin, Y. Pan, L. Zong, W. Feng, C.-H. Tan, K.-W. Huang, *Chem. Commun.* **2012**, *48*, 5479. (e) Y. Pan, C. W. Kee, Z. Jiang, T. Ma, Y. Zhao, Y. Yang, H. Xue, C.-H. Tan, *Chem. Eur. J.* **2011**, *17*, 8363. (f) X. Fu, Z. Jiang, C.-H. Tan, *Chem. Commun.* **2007**, 5058. (g) Z. Jiang, Y. Yang, Y. Pan, Y. Zhao, H. Liu, C.-H. Tan, *Chem. Eur. J.* **2009**, *15*, 4925. (h) L. Li, W. Chen, W. Yang, Y. Pan, H. Liu, C.-H. Tan, Z. Jiang, *Chem. Commun.* **2012**, *48*, 5124. (i) J. Wang, J. Chen, C. W. Kee, C.-H. Tan, *Angew. Chem. Int. Ed.* **2012**, *51*, 2382. (j) Y. Zhao, Y. Pan, H. Liu, Y. Yang, Z. Jiang, C.-H. Tan, *Chem. Eur. J.* **2011**, *17*, 3571. (k) W. Chen, W. Yang, L. Yan, C.-H. Tan, Z. Jiang, *Chem. Commun.* **2013**, *49*, 9854.