Organocatalysis

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Enantiodivergent and γ-Selective Asymmetric Allylic Amination**

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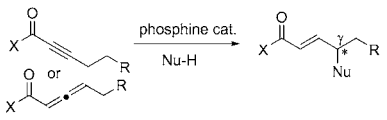
There are many readily available methods for the preparation of enantiopure carbonyl compounds containing α- and β-chiral centers. However, the selective functionalization of the γ position has been met with more difficulties and less progress. Asymmetric vinylogous aldol reactions,[1] Michael[2] reactions, and phosphine-catalyzed nucleophilic addition to alkynes and allenes [Eq. (1)][3] are some of the successful attempts made to address this difficult problem. In particular, the asymmetric vinylogous reactions seem to be most promising at delivering the desired results, despite the fact that the high electron density at the α position makes it kinetically favorable relative to the γ position. A cinchona-alkaloid-catalyzed direct enantioselective γ amination was reported using activated alkylidene cyanoacetates and malononitriles [Eq. (2); EWG = electron-withdrawing group].[4] Proline derivatives were also employed to catalyze the direct asymmetric γ functionalization of α,β-unsaturated aldehydes by transforming the electron-poor alkene into an electron-rich one [Eq. (3)].[5]



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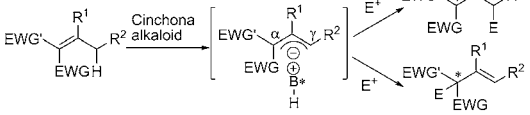

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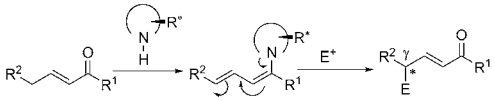
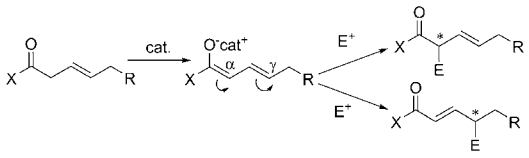


(3)

Enantiodivergent syntheses enable the preparation of both enantiomers utilizing the same chiral catalyst.[6] Metal-catalyzed enantiodivergent asymmetric catalysis can be achieved by tuning various parameters, including additive, counter ion, temperature, pressure, and solvent, used in the reactions.[7a] Few organocatalytic enantiodivergent reactions have been observed; however, several were reported for an asymmetric Baylis–Hilman reaction.[7b–d] In a recent example, a guanidine/bisthiourea-catalyzed Mannich-type reaction achieved a reversal of enantioselectivity by utilizing different solvent conditions.[8] Authors frequently include the following statements in their reports, "unexpected inversion of enantioselectivity", "change/dramatic change in the sense/direction of enantioselectivity", "switch of the expected chiral sense", and "unexpected reversal of the enantioselectivity". These statements imply that these enantiodivergent syntheses were not planned and it is difficult to design such reactions. It was reported that *E* and *Z* enolates exhibit different enantiofacial selectivities in enantioselective protonation reactions because the two diastereomeric transition states for the protonation of the *E* enolate are different from those for the *Z* enolate.[9] Accordingly, the four possible transition-state structures, resulting from the relative positioning of the substitutents, drive diastereomeric differentiation which leads to enantiodivergent selectivities of the protonation. We, thus, envisioned a reaction that leverages the *E*/*Z* geometry of a double bond to develop enantiodivergent asymmetric synthesis.

Guanidine derivatives were reported as efficient catalysts in asymmetric reactions.[10] Previously, we reported that a bicyclic guanidine effectively activates dithiomalonates in asymmetric Michael reactions.[11] The thioesters not only increased the acidity of α-hydrogen atoms of the nucleophiles, but also provided the substrate with a handle for modification. We hypothesized that with the help of an adjacent vinyl group, the acidity of the α-hydrogen atoms of unactivated thioesters might be additionally enhanced and facilitate deprotonation under mild reaction conditions (Scheme 1).[12] Both α-amination and γ-amination adducts are possible.



Scheme 1. Brønsted base catalyzed allylic addition.

We prepared substrate **1a** by a simple dicyclohexylcarbodiimide (DCC) coupling reaction of commercially available 3-hexenoic acid and 2-methyl-2-propanethiol. The reaction between the (*E*)-β,γ-unsaturated thioester **1a** and di-*tert*-butyl azodicarboxylate (**2c**) was slow and was not complete within 24 hours (Table 1, entry 1). However, we were pleased

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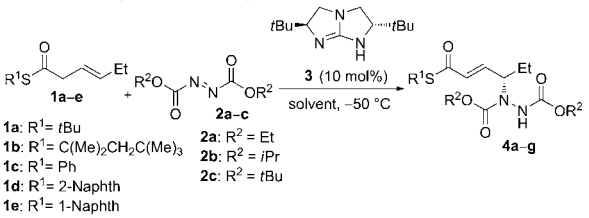
Table 1: γ-Selective direct allylic amination of (*E*)-β,γ-unsaturated thioesters with dialkyl azodicarboxylates.



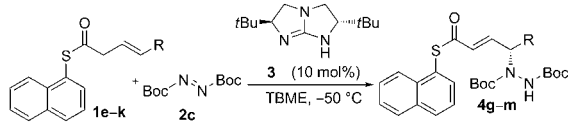
Entry	1	2	4	*t* [h]	Solvent	Yield [%][a]	*ee* [%][b]
1	**1a**	**2c**	**4a**	24	CH_2Cl_2	40	65
2	**1b**	**2c**	**4b**	24	CH_2Cl_2	30	67
3	**1c**	**2c**	**4c**	4	CH_2Cl_2	80	53
4	**1d**	**2c**	**4d**	4	CH_2Cl_2	85	69
5	**1e**	**2a**	**4e**	4	CH_2Cl_2	83	50
6	**1e**	**2b**	**4f**	4	CH_2Cl_2	84	58
7	**1e**	**2c**	**4g**	4	CH_2Cl_2	85	73
8	**1e**	**2c**	**4g**	4	$(iPr)_2O$	90	90
9	**1e**	**2c**	**4g**	4	MTBE	89	92

[a] Yield of isolated product. [b] Determined by HPLC analysis using a chiral stationary phase. Absolute configuration was determined by X-ray structure analysis of a derivative of **4** (see the Supporting Information).

to observe that only the γ-amination adduct was obtained and with an *ee* value of 65%. Several other (*E*)-β,γ-unsaturated thioesters were prepared and tested (entries 2–5). It was found that aromatic thioesters reacted with the azodicarboxylate at a significantly faster rate. The 1-napthyl thioester **1e** was thus chosen for additional optimization studies. Changing to other ether-type solvents such as diisopropyl ether (entry 8) and *tert*-butyl methyl ether (MTBE; entry 9) increased the enantioselectivity to greater than 90%.

The range of (*E*)-β,γ-unsaturated thioesters suitable for this reaction was investigated (Table 2). Unsaturated thioesters bearing different substituents at the γ position were evaluated under the same reaction conditions. With 10 mol% of the bicyclic guanidine **3**, all substrates tested gave only γ-amination adducts. Alkyl groups with different chain lengths (Table 2, entries 1–3), branched chains (entry 4), and bearing functionalized substitutents (entry 7) at the allylic position were investigated, and they all provided adducts in good yields and excellent enantioselectivities.

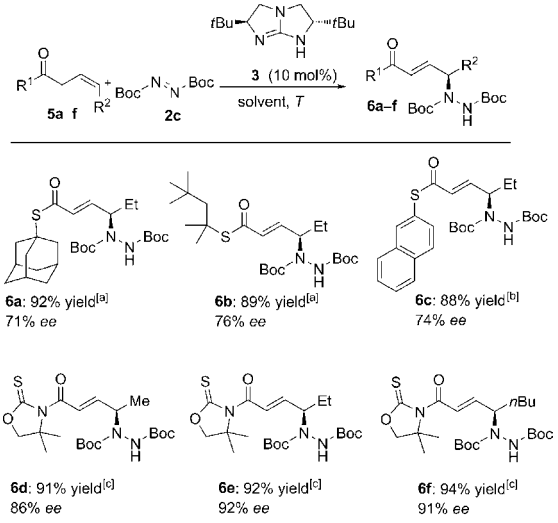
Table 2: γ-Selective direct allylic amination of (*E*)-β,γ-unsaturated 1-naphthyl thioesters with di-*tert*-butyl azodicarboxylate.



Entry	1	4	Yield [%][a]	*ee* [%][b]
1	**1e**: R = Et	**4g**	85	92
2	**1f**: R = Me	**4h**	86	86
3	**1g**: R = *n*Pr	**4i**	84	91
4	**1h**: R = *i*Pr	**4j**	89	96
5	**1i**: R = Bn	**4k**	87	93
6	**1j**: R = *n*Bu	**4l**	88	91
7	**1k**: R = CH_2OBn	**4m**	89	91

[a] Yield of isolated product after 4 h. [b] Determined by HPLC analysis using a chiral stationary phase. Absolute configuration was determined by independent synthesis and X-ray structure analysis of a derivative of **4** (see the Supporting Information). Bn = benzyl, Boc = *tert*-butoxycarbonyl.

To test the hypothesis that an enantiodivergent reaction can be obtained through the control of the double bond geometry, we decided to prepare (*Z*)-β,γ-unsaturated thioesters **5a–5c** (Scheme 2). Geometrically pure *Z* alkenes can

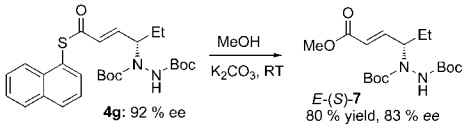


Scheme 2. γ-Selective direct allylic amination of (*Z*)-β,γ-unsaturated thioesters and acetyloxazolidinethiones with di-*tert*-butyl azodicarboxylate. [a] Et_2O, −20°C, yield of isolated product after 24 h. [b] MTBE, −50°C, yield of isolated product after 4 h. [c] *n*-Hexane, RT, yield of isolated product after 36 h.

be obtained from the corresponding alkynes through hydrogenation with the Lindlar catalyst. As we expected, adducts having the opposite configuration were obtained. However, only moderate enantioselectivity (71–76% *ee*) was observed. In our previous work with guanidine-catalyzed Mannich reactions, it was shown that β-keto acetyloxazolidinone resulted in a better level of enantioselectivity because of the additional opportunity for hydrogen bonding, compared with ester or thioester groups.[13] When the thioester group was replaced with 4,4-dimethyl-2-oxazolidinone, the reaction rate was too slow to be used. We, thus, made additional modifications to the auxiliary by using 4,4-dimethyloxazolidine-2-thione instead (**5d–f**; Scheme 2). A significant enhancement of the reaction rate and enantioselectivity was achieved. Up to 92% *ee* and good yields were achieved for the products **6d–f**. The limited substrate scope reported was mainly due to the limited range of commercially available 3-pentyn-1-ol derivatives. Other methods to prepare (*Z*)-β,γ-unsaturated acetyloxazolidinethiones are currently being explored.

Simple modification of the thioester **4g** and 4,4-dimethyloxazolidine-2-thione moiety of **6e** under mild methanolic conditions led to both enantiomers of the methyl esters (*E*)-**7** [Eq. (4) and Eq. (5)]. The opposite configurations of the methyl esters were confirmed using HPLC analysis with

a chiral stationary phase (see the Supporting Information). The absolute configuration of the products was established using X-ray structure analysis of a 4-chlorobenzene thioester, the benzoyl-protected hydrazine derivative of **4c** (see the Supporting Information).



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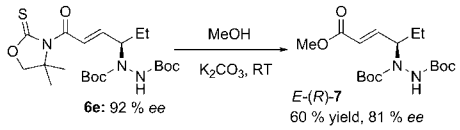
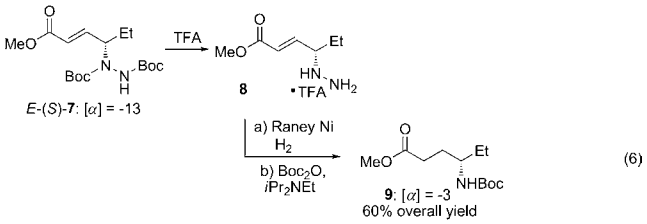


(5)

The γ-selective allylic amination products should have broad applications because of the possibility of enantiodivergent synthesis of the amino chiral center and the ease of modifying the neighbouring double bond. A simple and direct approach to preparing enantiopure γ-alkylated γ-aminoacids was demonstrated [Eq. (6); TFA = trifluoroacetic acid]. Three consecutive chiral centers, containing the 1,2-diol-3-amino group, is an challenging moiety to prepare. This moiety can be obtained by a highly diastereoselective OsO_4-promoted dihydroxylation [Eq. (7);NMO = *N*-methylmorpholine-*N*-oxide].



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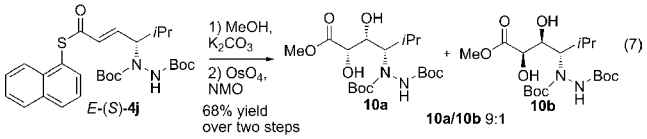


(7)

To gain insight into the reaction, density functional theory (DFT) calculations with the M06 functional[15] were performed. Transition-state (TS) structures based on a side-on model[16] previously reported by our group and a hetero-Diels–Alder (DA) mechanism proposed by Jørgensen[5a] were located. Amongst the 58 conformations located for the TS structures of both mechanisms (Figure 1), those based on the DA mechanism were higher in energy (9.5-32.4 kcal mol^{-1} relative to lowest-energy side-on TS) than those based on the side-on model. The DA TS structures are disfavored because of the weaker intermolecular interactions between dienolate and catalyst, and the 1,3-allylic strain in the s-*cis* dienolates.

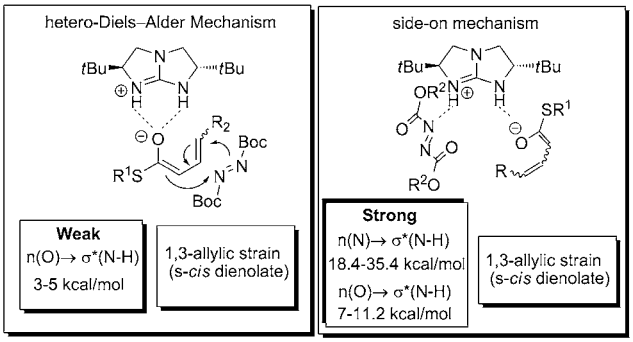
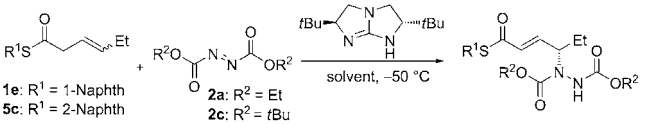


Figure 1. Plausible mechanisms. n(O) refers to the lone pair on the O of dienolate, n(N) refers to the lone pair on the N of diazocarboxylate. n(O)/n(N)→σ*(n-H) interaction energies are obtained from NBO analysis.[14]

Side-on TSs are stabilized by stronger intermolecular interactions, in particular the interaction between the lone pair of electrons on the N atom of the diazocarboxylate with the σ* of the N–H of the catalyst is especially strong. Side-on TSs based s-*cis* dienolates are generally higher in energy (5.3–26.3 kcal mol^{-1} relative to lowest-energy side-on TS) compared to those based on s-*trans* dienolates; this is expected because of the unfavourable 1,3-allylic interaction in the s-*cis* enolates.

The side-on mechanism based on s-*trans* dienolates was tested against the experimental results given in Table 1. The trend in change of enantioselectivity with solvent and substituents correlates well to $\Delta\Delta E^{+}$ (Table 3), thus validating the calculations. Analysis of the TS structures (Figure 2) revealed that the energetically less favorable TS in both the *E* and *Z* unsaturated thioester have the naphthyl substituent of the thioester in the same quadrant as the *t*Bu substituent of the catalyst, thus indicating that the destabilizing interaction between these two groups plays a major role in determining the relative energy of the transitions states leading to either *R* or *S* configurations, which is consistent with the result in Table 1. In contrast, the substituent on the C=C of the

Table 3: Comparison between DFT calculations and experimental results.



Reference	**1** or **5**	**2**	Solvent[a]	*ee* [%]	Expt. $\Delta\Delta G^{+}$	Calcd $\Delta\Delta E^{+}$[b]
Table 1, entry 5	**1e** (*E*)	**2a**	CH_2Cl_2	50	+0.5	+1.5
Table 1, entry 7	**1e** (*E*)	**2c**	CH_2Cl_2	73	+0.8	+1.7
Table 1, entry 8	**1e** (*E*)	**2c**	$(iPr)_2O$	90	+1.3	+2.1
Scheme 2	**5c** (*Z*)	**2c**	MTBE[c]	74	−0.8	−1.7

[a] Solvent effects were modeled with an IEFPCM calculation using radii and non-electrostatic terms for the Truhlar and co-workers' SMD solvation model.[14b] [b] $\Delta\Delta E^{+}$ (in kcal mol^{-1}) = $E_{TS,R} - E_{TS,S}$, *E* refers to the electronic energy of the TS structure at SMD-RM06[14a]/6-311++G-(2df,2p)//RM06/6-31G(d). [c] Single-point calculation was performed with iPr_2O instead of MTBE.

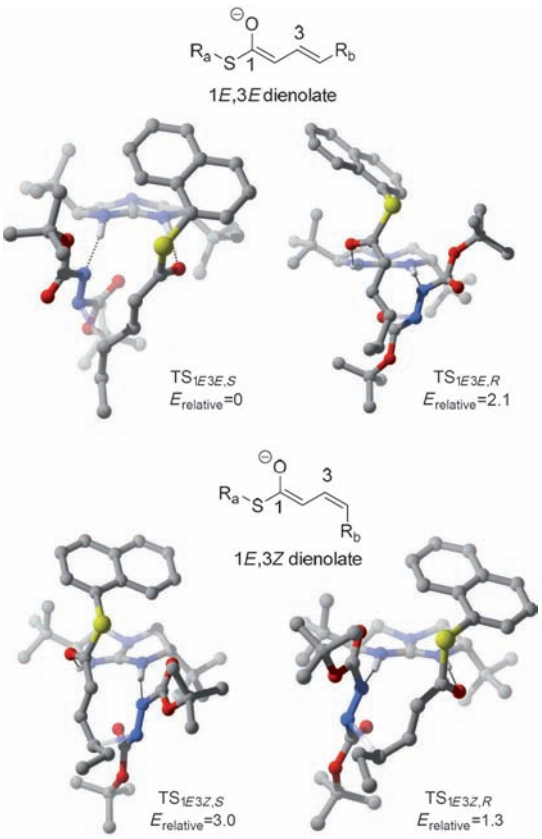


Figure 2. Most stable transition-state structures for side-on mechanism based on the s-*trans* dienolate calculated at the SMD-RM06/6-311++G(2df,2p)//RM06/6-31G(d) level of theory.

thioester is pointing away from the catalyst, and thus does not interact significantly with the catalyst. Its effect on the *ee* value should be minimal, and is consistent with the result in Table 2.

The inversion of the absolute configuration with the use of (*Z*)-β-unsaturated thioesters is also predicted by the side-on mechanism with the s-*trans* dienolate, $\Delta E^{\ddagger} = -1.7$ kcal mol^{-1}. It is consistent with both the inversion of the configuration and the lower *ee* value relative to the case in which the (*E*)-β-unsaturated thioesters were used (Table 3). Inversion of the absolute configuration is intuitively explained by the more stable TS having the 1-naphthyl substituent pointing away from the *t*Bu substituent of the catalyst. The TS for the *S* configuration satisfied this condition for the *E* thioester. As the *Z* thioester has the opposite configuration at the carbon at which the chiral center is formed, the TS with the 1-naphthyl pointing away from *t*Bu substituent of the catalyst became the TS with the *R* configuration, and hence inversion of the absolute configuration occurs.

In summary, we successfully developed a guanidine-catalyzed enantiodivergent γ-selective allylic amination. Both enantiomers can be obtained with excellent enantioselectivity and high yield. Computational studies suggest that the reaction proceeds through a side-on mechanism with an s-*trans* dienolate. The study agrees well with experimental results and provides an intuitive explanation for the inversion of the absolute configuration.

Experimental Section

Representative procedure for the γ-selective direct allylic amination of (*E*)-β,γ-unsaturated thioesters with dialkyl azodicarboxylates.

Dialkyl azodicarboxylate **2c** (11.5 mg, 0.10 mmol, 2.0 equiv) and **3** (1.1 mg, 0.005 mmol, 0.1 equiv) were dissolved in methyl *tert*-butyl ether (0.5 mL) and stirred at −50 °C for 20 min. (*E*)-β,γ-Unsaturated thioester **1** (13 mg, 0.05 mmol, 1.0 equiv) was then added. The reaction mixture was stirred at −50 °C and monitored by TLC. After the reaction was completed, as marked by the complete consumption of **1**, the reaction solvent was removed in vacuo. The crude reaction mixture was directly loaded onto a short silica gel column (gradient elution with *n*-hexane/ethyl acetate 20:1→7:1). After removing the solvent, the product **4** was obtained.

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[1] S. E. Denmark, G. L. Beutner, *J. Am. Chem. Soc.* **2003**, *125*, 7800–7801.
[2] S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192–1194.
[3] a) S. W. Smith, G. C. Fu, *J. Am. Chem. Soc.* **2009**, *131*, 14231–14232; b) Y. K. Chung, G. C. Fu, *Angew. Chem.* **2009**, *121*, 2259–2261; *Angew. Chem. Int. Ed.* **2009**, *48*, 2225–2227; c) J. W. Sun, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 4568–4569; d) R. Sinisi, J. Sun, G. C. Fu, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20652–20654.
[4] T. B. Poulsen, C. Alemparte, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 11614–11615.
[5] a) S. Bertelsen, M. Marigo, S. Brandes, P. Diner, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980; b) G. Bencivenni, P. Galzerano, A. Mazzanti, G. Bartoli, P. Melchiorre, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642–20647; c) G. Bergonzini, S. Vera, P. Melchiorre, *Angew. Chem.* **2010**, *122*, 9879–9882; *Angew. Chem. Int. Ed.* **2010**, *49*, 9685–9688.
[6] a) M. P. Sibi, M. Liu, *Curr. Org. Chem.* **2001**, *5*, 719–755; b) G. Zanoni, F. Castronovo, M. Franzini, G. Vidari, E. Giannini, *Chem. Soc. Rev.* **2003**, *32*, 115–129; c) M. Bartók, *Chem. Rev.* **2010**, *110*, 1663–1705.
[7] a) Y. H. Kim, *Acc. Chem. Res.* **2001**, *34*, 955–962; b) J. E. Imbriglio, M. M. Vasbinder, S. J. Miller, *Org. Lett.* **2003**, *5*, 3741–3743; c) S. H. Chen, B. C. Hong, C. F. Su, S. Sarshar, *Tetrahedron Lett.* **2005**, *46*, 8899–8903; d) N. Abermil, G. Masson, J. Zhu, *Org. Lett.* **2009**, *11*, 4648–4651.
[8] Y. Sohtome, S. Tanaka, K. Takada, T. Yamaguchi, K. Nagasawa, *Angew. Chem.* **2010**, *122*, 9440–9443; *Angew. Chem. Int. Ed.* **2010**, *49*, 9254–9257.
[9] C. Fehr, *Angew. Chem.* **1996**, *108*, 2726–2748; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2566–2587.
[10] Selected recent examples: a) H. Ube, N. Shimada, M. Terada, *Angew. Chem.* **2010**, *122*, 1902–1905; *Angew. Chem. Int. Ed.* **2010**, *49*, 1858–1861; b) T. Misaki, G. Takimoto, T. Sugimura, *J. Am. Chem. Soc.* **2010**, *132*, 6286–6287; c) S. Dong, X. Liu, X. Chen, F. Mei, Y. Zhang, B. Gao, L. Lin, X. Feng, *J. Am. Chem. Soc.* **2010**, *132*, 10650–10651; d) Y. Sohtome, B. Shin, N. Horitsugi, R. Takagi, K. Noguchi, K. Nagasawa, *Angew. Chem.* **2010**, *122*, 7457–7461; *Angew. Chem. Int. Ed.* **2010**, *49*, 7299–7303.
[11] Z. Jiang, W. Ye, Y. Zhao, S. L. M. Goh, D. Leow, Y.-T. Soh, C.-H. Tan, *Adv. Synth. Catal.* **2007**, *349*, 2454–2458.

[12] R. Yazaki, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 5522 – 5531.
[13] Y. Pan, Y. Zhao, T. Ma, Y. Yang, H. Liu, Z. Jiang, C.-H. Tan, *Chem. Eur. J.* **2010**, *16*, 779 – 782.
[14] a) Y. Zhao, D. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215 – 241; b) A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378 – 6396; c) Gaussian 09, Revision A.02, M. J. Frisch, et al., Inc., Wallingford CT, **2009**.
[15] NBO Version 3.1, E. D. Glendening, A. E. Reed, J. E. Carpenter, F. Weinhold.
[16] a) Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K. W. Huang, M. Wong, C.-H. Tan, *Angew. Chem.* **2009**, *121*, 3681 – 3685; *Angew. Chem. Int. Ed.* **2009**, *48*, 3627 – 3631; b) R. Lee, X. Lim, T. Chen, G. Tan, C.-H. Tan, K.-W. Huang, *Tetrahedron Lett.* **2009**, *50*, 1560 – 1562; c) X. Fu, C.-H. Tan, *Chem. Commun.* **2011**, *47*, 8210 – 8222; d) B. Cho, C.-H. Tan, M. W. Wong, *Org. Biomol. Chem.* **2011**, *9*, 4550 – 4557.