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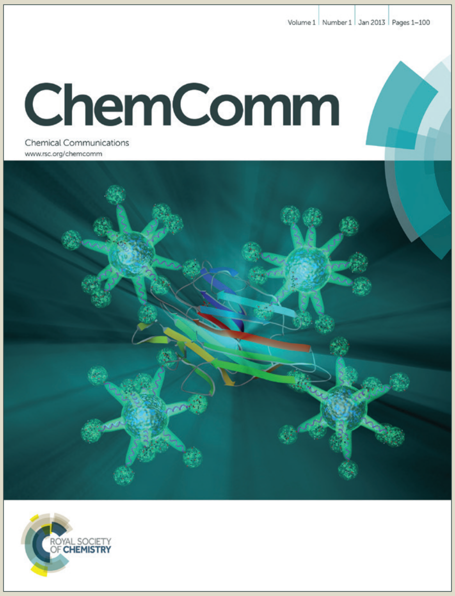

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ARTICLE TYPE

An unprecedented Pd-catalyzed *trans*-addition of boronic acids to ynamides

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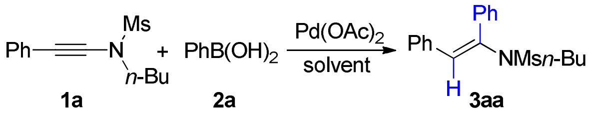
An unprecedented Pd-catalyzed *trans*-addition of boronic acids to ynamides has been reported, giving α,β-disubstituted enamides in high yields with excellent regio- and stereoselectivity. A possible mechanism involving the palladium carbene intermediate has been proposed to account for the unusual *trans*-addition.

Enamides are remarkably versatile building blocks in organic chemistry because they participate in a wide selection of chemical transformations.[1] Consequently, the interest in enamides has been long standing and the effective synthesis of these motifs, especially the stereocontrolled version, is still in urgent need. So far, enamides can be assembled by the isomerization of *N*-allylamides,[2] hydroamination of alkynes or alkenes,[3] methylenation of amides,[4] amidation of alkenyl halides or equivalents,[5] and C–H activation strategy.[6] Recently, the functionalization of ynamides, including silaboration,[7a] hydroboration,[7b] hydrophosphorylation,[7c] hydroacyloxylation,[7d] hydroamination,[7e] hydrohalogenation,[8] carbometallation,[9] cycloaddition,[10] and other reactions,[11] stands out as an attractive alternative protocol for accessing highly substituted enamides. On continuing our program geared towards the functionalization of ynamides,[12] we describe here a Pd-catalyzed stereospecific *trans*-addition of boronic acids to ynamides, providing stereodefined α,β-disubstituted enamides in high yields with excellent regio- and stereoselectivity. It should be noted that, although transition-metal-catalyzed addition of boronic acids to alkynes has become a powerful method for the assembly of multifunctional alkenes,[13] the Pd-catalyzed *trans*-hydroarylation of C–C triple bonds with boronic acids has not be reported before.[14]

The initial investigation began by screening the reaction conditions for hydroarylation of ynamide **1a** with $PhB(OH)_2$ (**2a**). When the reaction was conducted with 5 mol% of $Pd(OAc)_2$, 10 mol% of PPh_3, and 2 equiv of Na_2CO_3 in dioxane at 70 °C under nitrogen atmosphere for 5 h, a mixture of 80:20 *E*/*Z* isomers of **3aa** were obtained (Table 1, entry 1). Interestingly, the base was found to be unnecessary for the addition (Table 1, entries 2 and 3). A survey of solvents utilizing $P(3\text{-tol})_3$ as the ligand revealed that the readily accessible and environmentally friendly EtOH was the most effective, affording **3aa** as a single (*E*)-isomer in 93% yield (Table 1, entry 8). The regio- and stereochemistry of this reaction was unambiguously determined by the NOE and HMBC measurements (see ESI†). Other ligands such as PPh_3, PCy_3, dppe, and $P(4\text{-tol})_3$ provided inferior results (Table 1, entries 9–12). Therefore, the best reaction conditions for *trans*-addition of boronic acids to ynamides were affirmed as follows: 5 mol% of $Pd(OAc)_2$ and 10 mol% of $P(3\text{-tol})_3$ in EtOH under nitrogen atmosphere at 70 °C for 5 h.

Table 1. Screening of the reaction conditions[a]

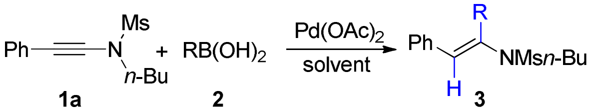


Entry	Ligand	Solvent	E/Z[b]	Yield (%)[c]
1[d]	PPh_3	Dioxane	80:20	67
2[d]	$P(3\text{-tol})_3$	Dioxane	86:14	71
3	$P(3\text{-tol})_3$	Dioxane	85:15	75
4	$P(3\text{-tol})_3$	DMF	95:5	82
5	$P(3\text{-tol})_3$	THF	89:11	78
6	$P(3\text{-tol})_3$	MeOH	95:5	88
7	$P(3\text{-tol})_3$	Toluene	98:2	91
8	$P(3\text{-tol})_3$	EtOH	>98:2	93
9	PPh_3	EtOH	75:25	62
10	PCy_3	EtOH	78:22	76
11	dppe	EtOH	38:62	56
12	$P(4\text{-tol})_3$	EtOH	96:4	87
13[e]	$P(3\text{-tol})_3$	EtOH	92:8	85

[a] Reaction conditions: **1a** (0.30 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), under N_2, 70 °C, 5 h. [b] Determined by GC. [c] Isolated yield. [d] 2 equiv of Na_2CO_3 was added. [e] Under air atomosphere.

Then, the scope of this *trans*-hydroarylation reaction was investigated by using different types of organoboron reagents (Table 2). Arylboronic acids possessing both electron-withdrawing and electron-donating substituents served as the good coupling partners in this process. Of note, the steric hindrance of **2** seemed to have no significant influence on the yield (Table 2, entries 1, 2, and 6–8). Gratifyingly, various functional groups such as F, CF_3, NO_2, Cl, OMe, CHO, Ac, CN, alkyl and aryl substituents were found to be compatible (Table 2, entries 1–16). Alkenyl boronic acids **2r** and **2s** furnished the 1,3-dienyl amides **3ar** and **3as** in good yields with excellent regio- and stereoselectivity (Table 2, entries 17 and 18). Moreover, the reaction was applicable to heteroarylboronic acids, as demonstrated by the reaction of **2t** and **2u** (Table 2, entries 19 and 20). Reaction of PhBpin (**2v**) performed well to generate **3aa** in satisfactory yield, while $MeB(OH)_2$ (**2w**) did not yield the desired product (Table 2, entries 21 and 22).

Table 2. Scope of boronic acids[a]



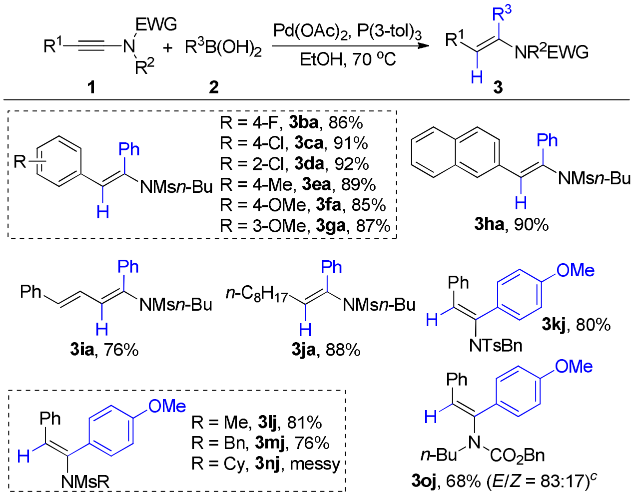
Entry	2	Yield (%)[b]
1	4-F-C_6H_4 (**2b**)	90 (**3ab**)
2	2,4-F_2-C_6H_3 (**2c**)	89 (**3ac**)
3	4-CF_3-C_6H_4 (**2d**)	84 (**3ad**)
4	3-NO_2-C_6H_4 (**2e**)	82 (**3ae**)
5	4-Cl-C_6H_4 (**2f**)	85 (**3af**)
6	4-Me-C_6H_4 (**2g**)	91 (**3ag**)
7	3-Me-C_6H_4 (**2h**)	91 (**3ah**)
8	2-Me-C_6H_4 (**2i**)	89 (**3ai**)
9	4-OMe-C_6H_4 (**2j**)	84 (**3aj**)
10	3,4-$(OMe)_2$-C_6H_3 (**2k**)	88 (**3ak**)
11	3,4-Methylenedioxyphenyl (**2l**)	92 (**3al**)
12	4-CHO-C_6H_4 (**2m**)	87 (**3am**)
13	4-MeCO-C_6H_4 (**2n**)	83 (**3an**)
14	4-CN-C_6H_4 (**2o**)	88 (**3ao**)
15	4-Ph-C_6H_4 (**2p**)	85 (**3ap**)
16	2-Naphthyl (**2q**)	86 (**3aq**)
17	(*E*)-1-Pentenyl (**2r**)	79 (**3ar**)
18	(*E*)-Styryl (**2s**)	70 (**3as**)
19	2-Thienyl (**2t**)	82 (**3at**)
20	2-Benzothiazolyl (**2u**)	77 (**3au**)
21	PhBpin (**2v**)	76 (**3aa**)
22	Me (**2w**)	NR

[a] Reaction conditions: see Table 1. [b] Isolated yield.

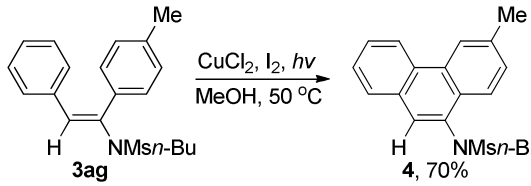
On the other hand, a variety of ynamides were successfully applied to the present *trans*-hydroarylation reaction. As shown in Table 3, both electron-poor and electron-rich ynamides **1b**–**g** reacted well to produce the corresponding enamides in excellent yields (Table 3, **3ba**–**ga**). Vinylic ynamide **1i** furnished dienyl enamide **3ia** in 76% yield, and substrate **1j**, with an alkyl chain, was also found to be well tolerated (Table 3, **3ia** and **3ja**). The *N*-Me and *N*-Bn substrates **1l** and **1m** provided **3lj** and **3mj** in high yields, while the *N*-Cy counterpart **1n** failed to produce the expected product, implying the steric effects of *N*-substituents of ynamides had some influence on this reaction (Table 3, **3lj**–**nj**). In contrast, ynamide **1o** provided the *trans*-addition product **3oj** in reduced stereoselectivity (Table 3, **3oj**). Additionally, when 3-(2-phenylethynyl)-2-oxazolidinone (**1p**) was subjected to the standard reaction conditions, only low conversion (<15%) was observed.

Next, we turned our attention to explore the synthetic utility of this protocol. When compound **3ag** was treated with 1 mol% of I_2 and 5 mol% of $CuCl_2$ in MeOH at 50 °C for 24 h,[12b] a phenanthrene derivative **4** was obtained in 70% yield upon isolation (eqn (1)).

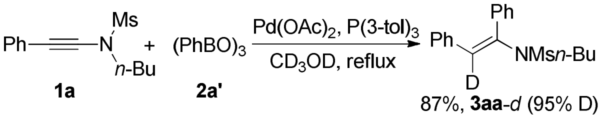
Table 3. Scope of ynamides[a,b]



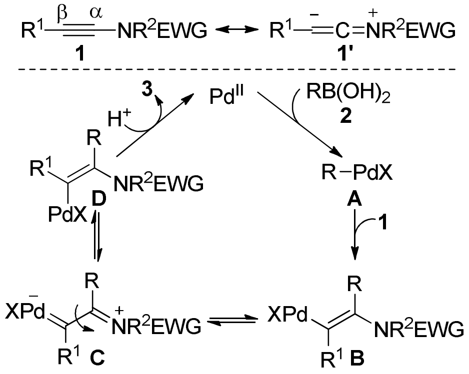
[a] Reaction conditions: see Table 1, 5–12 h. [b] Isolated yield. [c] Determined by GC.



(1)



(2)



Scheme 1. A possible mechanism.

Meanwhile, the deuteration experiments were conducted by reacting **1a** with $(PhBO)_3$ in CD_3OD at reflux for 5 h, and consequently, **3aa**-*d* was isolated in 87% yield with 95% deuterium incorporation (eqn (2)). Although the detailed mechanism for this unexpected *trans*-addition of boronic acids to ynamides is still unclear at current stage, a plausible mechanism is proposed in Scheme 1. Initially, an intermediate **A**, generated from transmetallation of Pd(II) with boronic acids **2**, undergoes the *cis*-carbopalladation with **1** to afford the species **B**. The highly polarized C–C triple bond of **1**, resulted from the electron donation by the nitrogen atom, may be responsible for controlling the regioselectivity of carbopalladation. Then, the *E*–*Z* isomerization[15,16] can take place via the palladium carbene species **C**, leading to the production of **D**. Finally, the protonolysis of alkenyl C–Pd bond[17] of **D** provides **3** and regenerates the Pd(II) catalyst (Scheme 1).

In summary, we have achieved a Pd-catalyzed stereospecific *trans*-addition of boronic acids to ynamides for the first time, furnishing α,β-disubstituted enamides in high yields with excellent regio- and stereoselectivity. The reaction operates under mild reaction conditions and a broad spectrum of functional groups are found to be well tolerated. Moreover, it allows a facile route to phenanthrene derivatives via the photochemical transformation of generated enamides. Further investigations on the reaction mechanism of *trans*-addition of boronic acids to ynamides are currently underway.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details and characterization of compounds **3** and **4**. See DOI: 10.1039/b000000x/

1 For selected reviews, see: (*a*) D. R. Carbery, *Org. Biomol. Chem.*, 2008, **6**, 3455. (*b*) K. Gopalaiah and H. B. Kagan, *Chem. Rev.*, 2011, **111**, 4599. (*c*) J.-H. Xie, S.-F. Zhu and Q.-L. Zhou, *Chem. Rev.*, 2011, **111**, 1713.

2 For a recent work, see: L. Wang, C. Liu, R. Bai, Y. Pan and A. Lei, *Chem. Commun.*, 2013, **49**, 7923 and references therein.

3 (*a*) M. Beller, J. Seayad, A. Tillack and H. Jiao, *Angew. Chem., Int. Ed.*, 2004, **43**, 3368. (*b*) J. M. Lee, D.-S. Ahn, D. Y. Jung, J. Lee, Y. Do, S. K. Kim and S. Chang, *J. Am. Chem. Soc.*, 2006, **128**, 12954. (*c*) N. Panda and R. Mothkuri, *J. Org. Chem.*, 2012, **77**, 9407.

4 N. A. Petasis and S.-P. Lu, *Tetrahedron Lett.*, 1995, **36**, 2393.

5 (*a*) R. Shen and J. A. Porco Jr, *Org. Lett.*, 2000, **2**, 1333. (*b*) L. Jiang, G. E. Job, A. Klapars and S. L. Buchwald, *Org. Lett.*, 2003, **5**, 3667. (*c*) X. Pan, Q. Cai and D. Ma, *Org. Lett.*, 2004, **6**, 1809. (*d*) H. Liu, Y. Zhou, X. Yan, C. Chen, Q. Liu and C. Xi, *Org. Lett.*, 2013, **15**, 5174. For a review, see: (*e*) J. R. Dehli, J. Legros and C. Bolm, *Chem. Commun.*, 2005, 973 and references therein.

6 (*a*) Y. Liu, D. Li and C.-M. Park, *Angew. Chem., Int. Ed.*, 2011, **123**, 7333. (*b*) H. Wang, L.-N. Guo and X.-H. Duan, *Org. Lett.*, 2012, **14**, 4358. (*c*) Y.-Y. Yu, M. J. Niphakis and G. I. Georg, *Org. Lett.*, 2011, **13**, 5932. (*d*) N. Gigant and I. Gillaizeau, *Org. Lett.*, 2012, **14**, 3304.

7 (*a*) N. Saito, K. Saito, H. Sato and Y. Sato, *Adv. Synth. Catal.*, 2013, **355**, 853. (*b*) B. Witulski, N. Buschmann and U. Bergsträßer, *Tetrahedron*, 2000, **56**, 8473. (*c*) A. Fadel, F. Legrand, G. Evano and N. Rabasso, *Adv. Synth. Catal.*, 2011, **353**, 263. (*d*) D. L. Smith, W. R. F. Goundry and H. W. Lam, *Chem. Commun.*, 2012, **48**, 1505. (*e*) S. Kramer, K. Dooleweerdt, A. T. Lindhardt, M. Rottländer and T. Skrydstrup, *Org. Lett.*, 2009, **11**, 4208.

8 (*a*) J. A. Mulder, K. C. M. Kurtz, R. P. Hsung, H. Coverdale, M. O. Frederick, L. Shen and C. A. Zificsak, *Org. Lett.*, 2003, **5**, 1547. (*b*) G. Compain, K. Jouvin, A. Martin-Mingot, G. Evano, J. Marrot and S. Thibaudeau, *Chem. Commun.*, 2012, **48**, 5196. (*c*) A. H. Sato, K. Ohashi and T. Iwasawa, *Tetrahedon Lett.*, 2013, **54**, 1309.

9 For the synthesis of enamides via carbopalladation of ynamides, see: (*a*) S. Couty, B. Liégault, C. Meyer and J. Cossy, *Org. Lett.*, 2004, **6**, 2511. (*b*) R. L. Greenaway, C. D. Campbell, O. T. Holton, C. A. Russell and E. A. Anderson, *Chem. Eur. J.*, 2011, **17**, 14366. (*c*) R. L. Greenaway, C. D. Campbell, H. A. Chapman and E. A. Anderson, *Adv. Synth. Catal.*, 2012, **354**, 3187. (*d*) B. Gourdet and H. W. Lam, *J. Am. Chem. Soc.*, 2009, **131**, 3802. (*e*) H. Yasui, H. Yorimitsu and K. Oshima, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 373. (*f*) H. Chechik-Lankin, S. Livshin and I. Marek, *Synlett*, 2005, 2098. (*g*) W. Gati, F. Couty, T. Boubaker, M. M. Rammah, M. B. Rammah and G. Evano, *Org. Lett.*, 2013, **15**, 3122. (*h*) A. Frischmuth and P. Knochel, *Angew. Chem., Int. Ed.*, 2013, **52**, 10084. For a review, see: (*i*) Y. Minko, M. Pasco, H. Chechik, I. Marek, *Beilstein J. Org. Chem.*, 2013, **9**, 526.

10 For recent works, see: (*a*) C. Schotes and A. Mezzetti, *Angew. Chem., Int. Ed.*, 2011, **50**, 3072. (*b*) H. Clavier, A. Lepronier, N. Bengobesse-Mintsa, D. Gatineau, H. Pellissier, L. Giordano, A. Tenaglia and G. Buono, *Adv. Synth. Catal.*, 2013, **355**, 403. (*c*) D. L. Smith, S. R. Chidipudi, W. R. Goundry and H. W. Lam, *Org. Lett.*, 2012, **14**, 4934.

11 For selected reports on the access of enamides via functionalization of ynamides since 2011, see: (*a*) S. Kramer, Y. Odabachian, J. Overgaard, M. Rottländer, F. Gagosz and T. Skrydstrup, *Angew. Chem., Int. Ed.*, 2011, **50**, 5090. (*b*) N. Saito, K. Saito, M. Shiro and Y. Sato, *Org. Lett.*, 2011, **13**, 2718. (*c*) R. B. Dateer, B. S. Shaibu and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 113. (*d*) E. Rettenmeier, A. M. Schuster, M. Rudolph, F. Rominger, C. A. Gade and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2013, **52**, 5880. (*e*) T. Nishimura, Y. Takiguchi, Y. Maeda and T. Hayashi, *Adv. Synth. Catal.*, 2013, **355**, 1374. (*f*) S. J. Heffernan, J. M. Beddoes, M. F. Mahon, A. J. Hennessy and D. R. Carbery, *Chem. Commun.*, 2013, **49**, 2314. (*g*) X.-N. Wang, G. N. Winston-McPherson, M. C. Walton, Y. Zhang, R. P. Hsung and K. A. DeKorver, *J. Org. Chem.*, 2013, **78**, 6233. (*h*) J. Brioche, C. Meyer and J. Cossy, *Org. Lett.*, 2013, **15**, 1626. (*i*) P. R Walker, C. D. Campbell, A. Suleman, G. Carr and E. A. Anderson, *Angew. Chem., Int. Ed.*, 2013, **52**, 9139. (*j*) Y. Kong, K. Jiang, J. Cao, L. Fu, L. Yu, G. Lai, Y. Cui, Z. Hu and G. Wang, *Org. Lett.*, 2013, **15**, 422.

12 (*a*) Z. Lu, W. Kong, Z. Yuan, X. Zhao and G. Zhu, *J. Org. Chem.*, 2011, **76**, 8524. (*b*) Z. Lu, W. Cui, S. Xia, Y. Bai, F. Luo and G. Zhu, *J. Org. Chem.*, 2012, **77**, 9871. (*c*) Z. Lu, X. Xu, Z. Yang, L. Kong and G. Zhu, *Tetrahedron Lett.*, 2012, **53**, 3433.

13 For Pd-catalyzed addition of boronic acids to alkynes, see: (*a*) C. H. Oh, H. H. Jung, K. S. Kim and N. Kim, *Angew. Chem., Int. Ed.*, 2003, **42**, 805. (*b*) N. Kim, K. S. Kim, A. K. Gupta and C. H. Oh, *Chem. Commun.*, 2004, 618. (*c*) H. Zeng and R. Hua, *J. Org. Chem.*, 2008, 73, 558. (*d*) X. Xu, J. Chen, W. Gao, H. Wu, J. Ding and W. Su, *Tetrahedron*, 2010, **66**, 2433. (*e*) Y. Bai, J. Yin, W. Kong, M. Mao, G. Zhu, *Chem. Commun.*, 2013, **49**, 7650. For other catalytic versions, see: (*f*) T. Hayashi, K. Inoue, N. Taniguchi and M. Ogasawara, *J. Am. Chem. Soc.*, 2001, **123**, 9918. (*g*) M. Lautens and M. Yoshida, *Org. Lett.*, 2002, **4**, 123. (*h*) J. Panteleev, R. Y. Huang, E. K. J. Lui and M. Lautens, *Org. Lett.*, 2011, **13**, 5314. (*i*) E. Genin, V. Michelet and J.-P. Genêt, *J. Organomet. Chem.*, 2004, **689**, 3820. (*j*) W. Zhang, M. Liu, H. Wu, J. Ding and J. Cheng, *Tetrahedron Lett.*, 2008, **49**, 5214. (*k*) A. Arcadi, M. Aschi, M. Chiarini, G. Ferrara and F. Marinelli, *Adv. Synth. Catal.*, 2010, **352**, 493. (*l*) B. Gourdet, D. L. Smith and H. W. Lam, *Tetrahedron*, 2010, **66**, 6026. (*m*) E. Shirakawa, G. Takahashi, T. Tsuchimoto and Y. Kawakami, *Chem. Commun.*, 2001, 2688. (*n*) P.-S. Lin, M. Jeganmohan and C.-H. Cheng, *Chem. Eur. J.*, 2008, **14**, 11296. (*o*) Y. Yamamoto, N. Kirai and Y. Harada, *Chem. Commun.*, 2008, 2010.

14 (*a*) C. Jia, W. Lu, J. Oyamada, T. Kitamura, K. Matsuda, M. Irie and Y. Fujiwara, *J. Am. Chem. Soc.*, 2000, **122**, 7252. (*b*) G. Zhang, Y. Peng, L. Cui and L. Zhang, *Angew. Chem., Int. Ed.*, 2009, **48**, 3112. (*c*) H Tsukamoto, T. Ueno and Y. Kondo, *J. Am. Chem. Soc.*, 2006, **128**, 1406.

15 (*a*) D. Zargarian and H. Alper, *Organometallics*, 1993, **12**, 712. For a recent report, see: (*b*) G.-P. Lu, K. R. Voigtritter, C. Cai and B. H. Lipshutz, *Chem. Commun.*, 2012, **48**, 8661.

16 The *E*-selectivity of product **3aa** determined at 20%, 45%, and 72% conversion was 90%, 95%, and >98% respectively, indicating that the stereoselectivity is controlled by thermodynamic effects.

17 G. Zhu, D. Chen, Y. Wang and R. Zheng, *Chem. Commun.*, 2012, **48**, 5796 and references therein.