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Protodeboronation of Tertiary Boronic Esters: Asymmetric Synthesis of Tertiary Alkyl Stereogenic Centers

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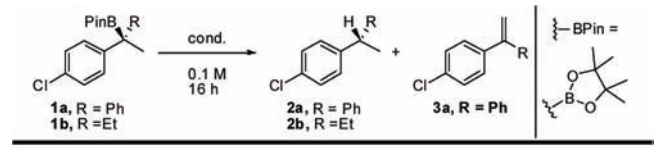
Abstract: While tertiary boranes undergo efficient protodeboronation with carboxylic acids, tertiary boronic esters do not. Instead, we have discovered that CsF with 1.1 equiv of H_2O (on tertiary diarylalkyl boronic esters) or TBAF·$3H_2O$ (on tertiary aryldialkyl boronic esters) effect highly efficient protodeboronation of tertiary boronic esters with essentially complete retention of configuration. Furthermore, substituting D_2O for H_2O provides ready access to deuterium-labeled enantioenriched tertiary alkanes. The methodology has been applied to a short synthesis of the sesquiterpene, (*S*)-turmerone.

Boronic esters are very useful synthetic intermediates in asymmetric synthesis since they can be easily prepared in high enantiomeric ratios (e.r.'s) by hydroboration[1] or rearrangement[2] reactions and can be converted with retention of configuration into alcohols or amines or used for C−C couplings.[1−3] We[4] (and others[5]) have recently reported a novel, practical method for the creation of tertiary boronic esters with very high e.r.'s (>98:2). We recognized that if we could convert the C−B bond of the tertiary boronic ester into a C−H bond this would provide ready access to a range of useful products including 1,1-diarylalkanes, which are privileged pharmacophores in medicinal chemistry but remain challenging to prepare.[6] However, protodeboronation of alkylboronic esters had not been described previously and in fact are reported to be stable to both acids and bases.[7]

The difficulties in protodeboronation are further compounded by the fact we are dealing with tertiary boronic esters which, by analogy with boranes, would be expected to be the slowest to protodeboronate.[8] Our initial attempts at protodeboronation of boronic ester **1a**, a compound likely to protodeboronate most readily, with the standard reagent used for boranes, propionic acid, were not promising: the desired alkane **2a** was obtained as the minor product in a 1:4 mixture together with alkene **3a** (Table 1, entry 1).

Propionic acid is the reagent of choice for effecting protodeboronation of boranes,[9] where the high free bond enthalpy of the newly formed B−O bond (536 kJ/mol) provides the driving force for the reaction (C−B bond energy 356 kJ/mol).[1a] Since B−F bonds are the strongest single bonds known[10] (B−F bond is 613 kJ/mol),[11] we reasoned that fluoride based reagents might prove more rewarding as they would provide an even greater driving force for protodeboronation. Thus, fluoride-based reagents were tested. Although HF led to a complex mixture (entry 2), CsF was much more successful. We found that excess water was detrimental to the reaction (entry 3),[12] but with just 1.1 equiv of H_2O clean protodeboronation at 100 °C was observed (entry 4). Through further optimization, we found conditions under which protodeboronation occurred in quantitative yield and with essentially complete enantioselectivity[13] (entry 5). TBAF was also tested but was found to be a much more aggressive reagent (reaction was much more rapid) and partial racemization of the fragile stereogenic center occurred (entry 6).

Table 1. Optimization of the Protodeboronation of Boronic Esters[a]



1a, R = Ph; **1b**, R = Et — **2a**, R = Ph; **2b**, R = Et — **3a**, R = Ph

Entry		Reagent[a]	Solvent	T(°C)	Conversion[b]	% es[c]
1	**1a**	$CH_3CH_2CO_2H$		130	37%[d]	n.d.
2	**1a**	HF aq. (48%)		20	88%[d]	n.d.
3	**1a**	CsF	Dioxane/ 5% H_2O	100	0%	-
4	**1a**	CsF, H_2O	Dioxane	100	99%	95%
5	**1a**	CsF, H_2O	Dioxane	45	99%	99%
6	**1a**	TBAF·$3H_2O$	Dioxane	20	99%	86%
7	**1b**	CsF, H_2O	Dioxane	100	22%	n.d.
8	**1b**	TBAF·$3H_2O$	Dioxane	45	99%	95%
9	**1b**	TBAF·$3H_2O$	Toluene	45	99%	99%
10	**1b**	TBAF·$3H_2O$	n-C_5H_{12}	45	99%	99%

[a] Standard reaction conditions: 0.1 M in given solvent, 1.5 equiv of CsF, 1.1 equiv of water or 1.5 equiv of TBAF·$3H_2O$. [b] Consumption of SM **1a**/**1b** determined by GC with tetradecane as internal standard. [c] % es = (product ee/starting material ee) × 100. Det. by chiral HPLC or chiral GC (see Supporting Information). [d] **3a**:**2a** = 3:1 (entry 1) respectively 4:1 (entry 2).

These initial studies greatly assisted our investigation into the protodeboronation of tertiary aryldialkyl boronic esters, which were expected to react more slowly. Indeed, CsF in dioxane, which was the optimum solvent for diarylalkyl boronic ester (R = Ph), resulted in very slow protodeboronation of aryldialkyl boronic ester **1b** even at 100 °C (entry 7, R = Et). In contrast, the more reactive reagent, TBAF, effected clean protodeboronation (entry 8) and without racemization when conducted in nonpolar solvents (entries 9−10).

Having established two sets of conditions (A and B) for effective protodeboronation of diarylalkyl and aryldialkyl tertiary boronic esters, we investigated the scope of the methodology with a diverse range of substrates that were readily obtained through the lithiation−borylation reaction of secondary carbamates[4] (Table 2). In the case of diarylalkyl boronic esters, the reaction was successfully applied to aromatic substrates bearing electron-deficient, electron-rich, and heteroaromatic groups. Minor adjustments to the temperature of the reaction were required according to the ease/difficulty of the protodeboronation process (Table 2, entries 1−4). Substrates bearing anion stabilizing groups underwent protodeboronation more easily and so lower temperatures could be employed. Conditions B were also successfully applied to a related set of

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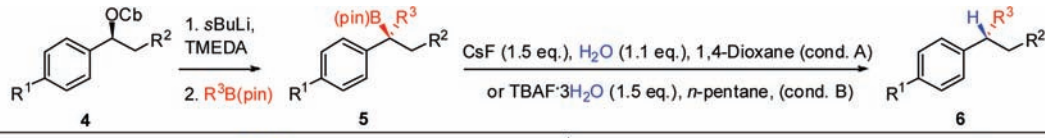
Table 2. Investigation into the Scope of the Reaction[a]



4 5 6

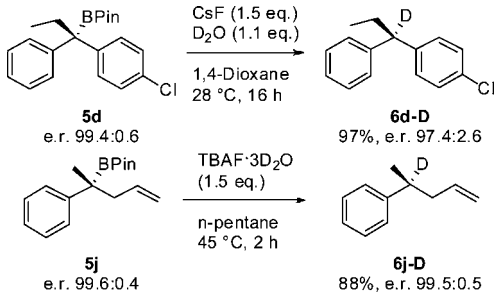
Entry	R^1	R^2	e.r. of carbamate	R^3	5[b] yield	5[b] e.r.	Conditions[c]	6 yield	6 e.r.	% es
1	H	H	**4a** 99.9:0.1	*p*-ClC_6H_4	**5a** 89%	99.7:0.3	A, 30 °C	**6a** 82%	97.3:2.7	98%
2	OMe	H	**4b** 99.5:0.5	Ph	**5b** 85%	98.3:1.7	A, 65 °C	**6b** 99%	98.1:1.9	99%
3	H	H	**4a** 99.9:0.1	2-furyl	**5c** 79%	99.0:1.0	A, 35 °C	**6c** 99%	97.9:2.1	98%
4	H	Me	**4c** 99.9:0.1	*p*-ClC_6H_4	**5d** 71%	99.4:0.6	A, 30 °C	**6d** 91%	98.7:1.3	99%
5	H	H	**4a** 99.9:0.1	Et	**5e** 68%	99.7:0.3	B, 45 °C	**6e** 97%	98.8:1.2	99%
6	Cl	H	**4d** 99.6:0.4	Et	**5f** 83%	99.4:0.6	B, 45 °C	**6f** 99%	98.9:1.1	99%
7	OMe	H	**4b** 99.9:0.1	Et	**5g** 88%	99.9:0.1	B, 45 °C	**6g** 90%	99.8:0.2	99%
8	H	H	**4a** 99.5:0.5	^{i}Pr	**5h** 98%	99.5:0.5	B, 45 °C	**6h** 96%	99.2:0.8	99%
9	H	H	**4e** *rac*	Vinyl	**5i** 57%	*rac*	B, 30 °C	**7** 91%	*E*:*Z* > 20:1[d]	-
10	H	H	**4a** 99.9:0.1	Allyl	**5j** 91%	99.6:0.4	B, 45 °C	**6j** 98%	99.5:0.5	99%
11	H	Me	**4c** 99.9:0.1	Allyl	**5k** 59%	99.9:0.1	B, 30 °C	**6k** 79%	99.9:0.1	99%

[a] All yields are isolated yields unless stated otherwise. E.r. was determined by chiral HPLC or chiral GC (see Supporting Information). [b] E.r. of the alcohol resulting from oxidation of the boronic ester with $NaOH/H_2O_2$. [c] Conditions: (A) CsF (1.5 equiv), H_2O (1.1 equiv), 1,4-dioxane (0.1 M); (B) TBAF·$3H_2O$ (1.5 equiv), *n*-pentane (0.1 M), 45 °C, 2 h. [d] **7** = *E*-2-Phenyl-2-butene.

aryldialkyl boronic esters (entries 5−12). Particularly noteworthy is the β-branched substrate (entry 8) which demonstrates that this novel process shows broad scope since it tolerates even severe steric hindrance. Note, although toluene was the optimum solvent, pentane was found to be more practical as it facilitated the isolation of especially volatile products. The only substrate that failed (as expected) was the one employing vinyl boronic ester in the borylation step (entry 9) since the intermediate *allyl* boronic ester **5i** underwent protodeboronation at the γ position forming *E* alkene **7** exclusively. Use of allyl boronic ester in the borylation step (entries 10, 11) gave intermediate homoallylic boronic esters **5j** and **5k** which, as expected, underwent smooth protodeboronation at the α position. In all cases, protodeboronation occurred with retention of configuration.

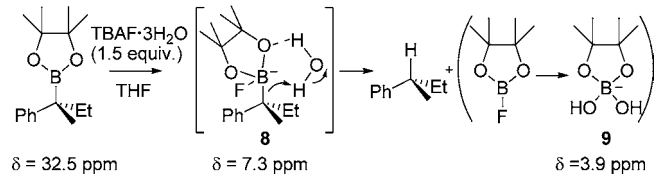
The methodology provides a unique protocol for the introduction of deuterium by simply substituting H_2O for D_2O, as demonstrated by two representative examples (Scheme 1).

Scheme 1. Deuterodeboronation of Tertiary Boronic Esters



A possible mechanism, analogous with the cyclic rearrangement leading to protodeboronation of boranes, is shown in Scheme 2. In nonprotic media, the water will interact strongly with fluoride ion both prior to and after formation of ate complex **8**, ensuring 'front-side' proton delivery and hence stereoretention. Under certain conditions the degree of stereoretention was not perfect (Table 1,

Scheme 2. Mechanism of Protodeboronation of Tertiary Boronic Esters

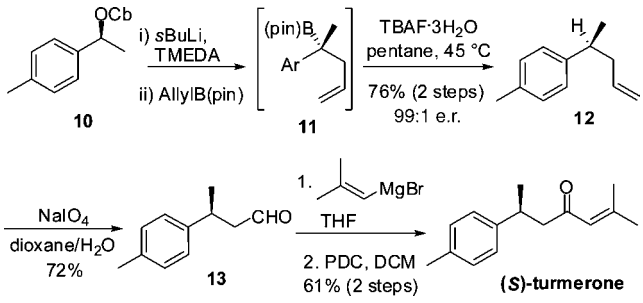


entries 4, 6, and 8), and so further investigations were conducted. Protodeboronation of **1a** with TBAF (Table 1, entry 6) was monitored over 12 h, but no change in ee was observed; it remained constant at 70%.[14] This showed that the lower enantioselectivity observed under such conditions was due to a competing inversion pathway during protodeboronation and not due to product lability. The competing inversion pathway will be more important in polar solvents, where water will be less tightly bound to the ate complex and so will lead to lower e.r., as observed (compare entries 8, 9, Table 1).

In order to obtain a more complete picture of the protodeboronation process, we monitored the reaction by ^{11}B NMR in THF at RT. Immediately after addition of TBAF, the signal for the starting boronic ester disappeared (δ = 32.5 ppm) and a new signal at δ = 7.3 ppm appeared, which we believe corresponds to the intermediate ate complex **8**.[15] Over time, this signal slowly decayed and a new signal at 3.9 ppm grew in intensity. We believe that this peak corresponds to the dihydroxy borate byproduct **9** (δ = 3.9 ppm).[16] The initial byproduct formed in the reaction, FBpin, is not expected to be stable to the hydrolytic conditions of the reaction.[17] These studies demonstrate that the intermediate ate complex **8** is observable in THF and its decay can be followed by NMR.

Finally, the methodology was applied to a short synthesis of (*S*)-turmerone (Scheme 3), a sesquiterpene isolated from rhizomes of *curuma longa*,[18] which has been a popular target for the synthetic community. However, there have been very few enantioselective syntheses reported to date.[19] Our synthesis commenced with enantioenriched (*S*)-carbamate **10**, derived from the corresponding

Scheme 3. Total Synthesis of (*S*)-Turmerone



alcohol,[20] which was subjected to lithiation with 1.2 equiv of *sec*-BuLi in the presence of TMEDA for 10 min. Subsequent reaction with 1.5 equiv of allyl pinacol boronic ester furnished the tertiary boronic ester **11**, which was used in the key protodeboronation step without further purification. Treatment of **11** with 1.5 equiv of TBAF·$3H_2O$ in pentane at 45 °C smoothly afforded the protodeboronated product **12**, installing the benzylic tertiary center in excellent yield (76% over two steps) and selectivity (99:1 e.r.). Finally, oxidation[21] of alkene **12** to aldehyde **13** followed by addition of 2-methyl-1-propenylmagnesium bromide and subsequent oxidation with PDC furnished the target compound, (*S*)-turmerone. The synthesis was completed in seven steps from *p*-methylacetophenone and delivered the target compound in (99:1 e.r.).

In conclusion, we have discovered a new and simple way to effect protodeboronation of boronic esters using CsF-H_2O or TBAF·$3H_2O$ with essentially complete stereocontrol, thus providing ready access to enantioenriched tertiary alkanes.[22] The method also provides access to highly enantioenriched deuterated tertiary alkanes by simply substituting H_2O for D_2O. The utility of the methodology has been illustrated in a short and highly enantioselective synthesis of (*S*)-turmerone.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer: Berlin, 1995. (b) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695–4712.

(2) (a) Matteson, D. S. *Acc. Chem. Res.* **1988**, *21*, 294–300. (b) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555–10607. (c) Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. *Chem. Rec.* **2009**, *9*, 24–39. (d) Aggarwal, V. K.; Fang, G. Y.; Schmidt, A. T. *J. Am. Chem. Soc.* **2005**, *127*, 1642–1643. (e) Stymiest, J.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 7491–7494. (f) Dutheuil, G.; Webster, M. P.; Worthington, P. A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 6317–6319.

(3) (a) Brown, H. C.; Singaram, B. *Pure Appl. Chem.* **1987**, *59*, 879. (b) *Science of Synthesis: Vol. 6 Boron Compounds*; Kaufmann, D. E., Matteson, D. S., Eds.; Georg Thieme Verlag: Stuttgart-New York, 2004. (c) Hall, D. G. *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 1−85. Recent examples for C−C coupling using aliphatic pinacol boronic esters: (d) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024–5025. (e) Ros, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 6289–6292.

(4) (a) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778–783. (b) Bagutski, V.; French, R. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5142–5145.

(5) (a) Chen, I.-H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664–11665. (b) Lee, K.; Zhugralin, A.; Hoveyda, A. *J. Am. Chem. Soc.* **2009**, *131*, 7253. (c) O'Brien, J. M.; Lee, K.-S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630–10633. (d) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634–10637.

(6) (a) O'Shea, P. D.; Chen, C.-Y.; Chen, W.; Dagneau, P.; Frey, L. F.; Grabowski, E. J. J.; Marcantonio, K. M.; Reamer, R. A.; Tan, L.; Tillyer, R. D.; Roy, A.; Wang, X.; Zhao, D. *J. Org. Chem.* **2005**, *70*, 3021–3030. (b) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9331–9334. (c) Kleemann, A. *Pharmaceutical substances: Syntheses, Patents, Applications*, 4th ed.; Thieme: Stuttgart, 2001.

(7) (a) Matteson, D. S. *J. Organomet. Chem.* **1999**, *581*, 51–65. Renaud has discovered an unusual (nonselective) protodeboronation of catechol boronic esters in the presence of methanol. (b) Pozzi, D.; Scanlan, E.; Renaud, P. *J. Am. Chem. Soc.* **2005**, *127*, 14204–14205. (c) Povie, G.; Villa, G.; Ford, L.; Pozzi, D.; Schiesser, C. H.; Renaud, P. *Chem. Commun.* **2010**, *46*, 803–805.

(8) The relative rates of protodeboronation of boranes are 1 (primary):0.052 (secondary):∼0 (tertiary). See: Brown, H. C.; Murray, K. J. *Tetrahedron* **1986**, *42*, 5497–5504. However, the presence of aromatic groups should promote protodeboronation and so will temper the inherently slow rate associated with tertiary boronic esters. See: Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1959**, *81*, 1512.

(9) Brown, H. C.; Marray, K. J. *Tetrahedron* **1986**, *42*, 5497–5504.

(10) Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*; Butterworth-Heineman: Oxford, 1997; pp 196.

(11) Bond enthalpy data were taken from (accessed on 8/25/2010) http://www.wiredchemist.com/chemistry/data/bond_energies_lengths.html.

(12) The reactivity of fluoride in organic solution is fundamentally dependent on the water content: Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050–2051.

(13) The term enantiospecificity has been used to describe the conservation of optical purity over the course of stereospecific reactions: (a) Denmark, S. E.; Vogler, T. *Chem.—Eur. J.* **2009**, *15*, 11737. (b) Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191–13193.

(14) The ee of **1a** after 15 min, 1 h, 2 h, 5 h, and 12 h was 70% in all cases.

(15) Typical chemical shifts in ^{11}B NMR of $Bu_4NArB(pin)F$ in THF are around δ 7.0 ppm. Oehlke, A.; Auer, A. A.; Schreiter, K.; Hofmann, K.; Riedel, F.; Spange, S. *J. Org. Chem.* **2009**, *74*, 3316–3322, and references therein.

(16) Henderson, W. G.; How, M. J.; Kennedy, G. R.; Mooney, E. F. *Carbohydr. Res.* **1973**, *28*, 1–12.

(17) Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5156–5160.

(18) (a) *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck & Co.: Rahway, NJ, 1996; pp 1674−1675. (b) Rupe, H.; Gassman, A. *Helv. Chim. Acta* **1936**, *19*, 569.

(19) (a) Meyers, A. I.; Smith, R. K. *Tetrahedron Lett.* **1979**, *30*, 2749. (b) Rowe, B. J.; Spilling, C. D. *J. Org. Chem.* **2003**, *68*, 9502. (c) Fuganti, C.; Serra, S.; Dulio, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 279. (d) Zhang, A.; Rajanbabu, T. *Org. Lett.* **2004**, *6*, 3159. (e) Kamal, A.; Malik, M.; Azeeza, S.; Bajee, S.; Shaik, A. *Tetrahedron: Asymmetry* **2009**, *20*, 1267–1271.

(20) For details, see Supporting Information.

(21) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Zhendong, G. *Org. Lett.* **2004**, *6*, 3217.

(22) For alternative methods see: (a) Wilsily, A.; Nguyen, Y.; Fillion, E. *J. Am. Chem. Soc.* **2009**, *131*, 15606–15607. (b) López-Pérez, A.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 5514–5517. (c) Hedberg, C.; Kallstrom, K.; Brandt, P.; Hansen, K.; Andersson, P. *J. Am. Chem. Soc.* **2006**, *128*, 2995–3001. (d) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402–1411. (e) Lee, Y.; Li, B.; Hoveyda, A. *J. Am. Chem. Soc.* **2009**, *131*, 11625–11633. (f) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. *J. Am. Chem. Soc.* **2008**, *130*, 446–447. (g) Kacprzynski, M.; Hoveyda, A. *J. Am. Chem. Soc.* **2004**, *126*, 10676–10681. (h) Langlois, J.-B.; Alexakis, A. *Chem. Commun.* **2009**, 3868–3870. (i) Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765–378. (j) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272–3296. (k) Tolstoy, P.; Engman, M.; Patptchikhine, A.; Bergquist, J.; Church, T.; Leung, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8855–8860. (l) Sörgel, S.; Tokunaga, N.; Sasaki, K.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2008**, *10*, 589–592. (m) Duan, H.; Meng, L.; Bao, D.; Zhang, H.; Li, Y.; Lei, A. *Angew. Chem., Int. Ed.* **2010**, *49*, DOI: 10.1002/anie.201002116.

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