

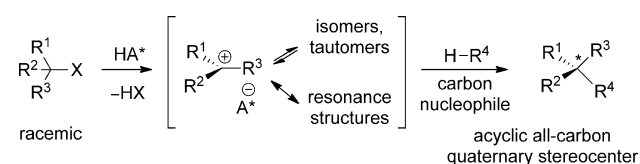
Enantioselective Formation of All-Carbon Quaternary Stereocenters from Indoles and Tertiary Alcohols Bearing A Directing Group**

Wanxiang Zhao, Zhaobin Wang, Boyang Chu, and Jianwei Sun*

Abstract: Described is an efficient catalytic asymmetric intermolecular C–C bond-formation process to generate acyclic all-carbon quaternary stereocenters. The reactions overcome the unfavorable steric hindrance around reactive centers, and the competitive elimination (E1), to form a range of useful indole products with excellent efficiency and enantioselectivity.

Efficient formation of quaternary stereocenters is a long-standing topic in organic synthesis.^[1] Among them, all-carbon quaternary stereocenters represent a particularly challenging structural element to assemble.^[2] The difficulty further increases for acyclic quaternary systems in intermolecular reactions as a result of the increased structural flexibility and activation barrier.^[2a]

In the past decade, various catalytic asymmetric systems have been developed to address the above challenges.^[2] Among them, direct asymmetric nucleophilic substitution between a racemic tertiary alkyl electrophile and a carbon-based nucleophile, by means of formal S_N1 pathway (Scheme 1), proved attractive, but was realized with limita-



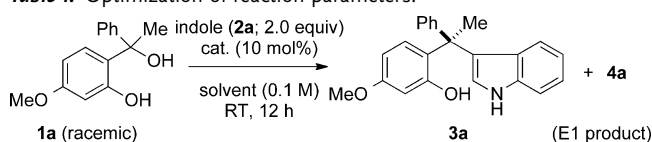
Scheme 1. Asymmetric nucleophilic substitution of racemic tertiary electrophiles.

tions.^[3] All these examples employ indol-3-yl-substituted electrophiles, which are typically proposed to proceed via the corresponding extended iminium ions. Moreover, the hypothetical tertiary carbocation intermediates are all substituted with either aryl or electron-withdrawing groups without β -hydrogen atoms, thereby inhibiting the competing E1 process and avoiding the chemoselectivity issue. Nevertheless, these pioneering studies have significantly advanced this area of research.^[4] Inspired by them, we report herein the

efficient formation of acyclic all-carbon quaternary stereocenters with non-indol-3-yl-type tertiary alkyl electrophiles.

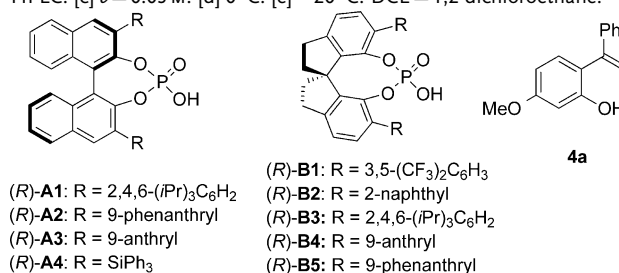
After some effort, we were pleased to find that the racemic tertiary alcohol **1a** is a suitable electrophile. Indole (**2a**) was employed as the carbon nucleophile since it represents a family of versatile building blocks in organic synthesis as well as useful subunits in natural products and biologically active molecules.^[5] Furthermore, inspired by the wide success of chiral phosphoric acids in asymmetric catalysis^[6] as well as our previous effort in this area,^[7] we evaluated them for this reaction. Encouragingly, the BINOL-derived phosphoric acids **A1–A3** all gave excellent conversion to the desired product **3a**, albeit with disappointing enantioselectivity (Table 1, entries 1–3). The use of **A4**,

Table 1: Optimization of reaction parameters.



Entry	Cat.	Solvent	3 a/4 a ^[a]	Yield [%] ^[a]	ee [%] ^[b]
1	A1	CH ₂ Cl ₂	> 20:1	77	–37
2	A2	CH ₂ Cl ₂	> 20:1	85	–53
3	A3	CH ₂ Cl ₂	> 20:1	91	–40
4	A4	CH ₂ Cl ₂	1.3:1	47	–72
5	B1	CH ₂ Cl ₂	> 20:1	81	66
6	B2	CH ₂ Cl ₂	> 20:1	76	70
7	B3	CH ₂ Cl ₂	1.3:1	37	42
8	B4	CH ₂ Cl ₂	> 20:1	80	73
9	B5	CH ₂ Cl ₂	> 20:1	87	80
10	B5	CHCl ₃	> 20:1	62	69
11	B5	DCE	> 20:1	81	83
12	B5	toluene	> 20:1	81	76
13	B5	Et ₂ O	4.5:1	63	24
14	B5	DCE ^[c]	> 20:1	82	85
15 ^[d]	B5	DCE ^[c]	> 20:1	87	92
16 ^[e]	B5	DCE ^[c]	> 20:1	55	88

[a] The ratio and yield were based on ¹H NMR spectra of the crude reaction mixture with CH₂Br₂ as the internal standard. [b] Determined by HPLC. [c] c = 0.05 M. [d] 0 °C. [e] –20 °C. DCE = 1,2-dichloroethane.



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bearing a bulky SiPh₃ substituent, improved the enantioselectivity, but the desired product was obtained in a significantly lower yield (47%). Indeed, the E1 product alkene **4a** accounts for the remainder of the mass balance, presumably as a result of the significant steric bulk, which prevents the nucleophile from approaching the reactive center. We next resorted to the chiral acids **B1–B5** with the spirocyclic backbone. Fortunately, **B5** catalyzed the reaction with both good chemical efficiency and enantioselectivity (entry 9). Further solvent screening indicated that solvents can dramatically influence the enantioselectivity (entries 10–13). DCE was identified as the solvent of choice (entry 11). Lowering the reaction temperature (to 0 °C) and the concentration (to 0.05 M) resulted in the best efficiency and enantioselectivity (entry 15).

Next, we examined the reaction scope (Table 2). A range of indoles participated smoothly in the mild C–C bond

Table 2: Scope with respect to the indole.

Entry	R	3	Yield [%] ^[a]	ee [%]
1	H	3a	98 ^[b]	91 ^[b]
2	5-Me	3b	99	90
3	5-OMe	3c	82	84
4	5-OBn	3d	90	84
5	5-Br	3e	95	95
6	5-CO ₂ Me	3f	81	96
7	6-Me	3g	97	82
8	6-Br	3h	83	90
9	6-F	3i	90	92
10	7-Me	3j	87	58

[a] Yield of isolated product. [b] The results are the average of two runs, with (R)- and (S)-**B5**, respectively.

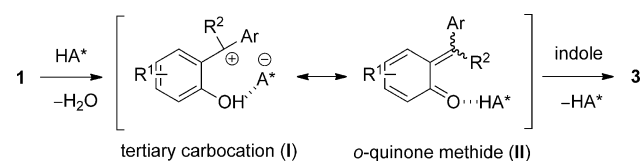
formation to form the all-carbon quaternary stereocenters with good to excellent efficiency and enantioselectivity. Indoles substituted at the 2- and 4-positions resulted in low reactivity, which is likely due to the steric hindrance adjacent to the reactive 3-position. The standard protocol is also effective for a range of other tertiary alcohols (Table 3). The mild reaction conditions can tolerate a variety of functional groups, such as ethers, silyl-protected alcohols, alkenes, alkynes, etc. Heterocycles such as thiophene can also be incorporated into the products. It is worth noting that the reaction is limited to electron-rich phenols bearing a methyl group at the benzylic position. In the case of an ethyl-substituted alcohol, **B5** proved inferior for stereocontrol, but fortunately **A4** could catalyze the desired transformation with promising enantioselectivity (entry 12). Notably, in all these cases the desired substitution pathway is dominant (versus E1).

We have proposed a possible mechanism (Scheme 2). The reaction starts with protonation of the alcohol **1** and subsequent C–O cleavage to generate the tertiary carbocation **I**,

Table 3: Scope with respect to the tertiary alcohols.

Entry	1	3	Yield [%] ^[a]	ee [%]
1		3k	83	94
2		3l	47 ^[b]	91
3		3m	88	97
4		3n	90	91
5		3o	97	90
6		3p	86	95
7		3q	92	95
8		3r	99	92
9		3s	92	94
10		3t	83	93
11		3u	93	80
12		3v	62	–70 ^[c]
13		3w	77	86

[a] Yield of the isolated product. [b] The E1 product alkene accounts for remainder of the mass balance. [c] (R)-**A4** was used as catalyst and (R)-**3v** was formed. TBS = *tert*-butyldimethylsilyl.

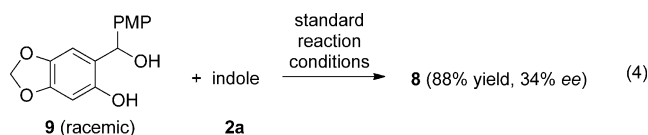
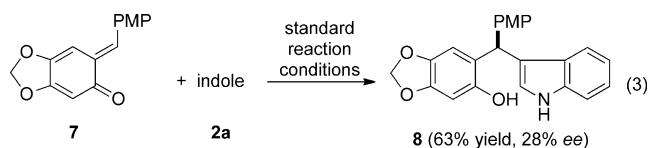
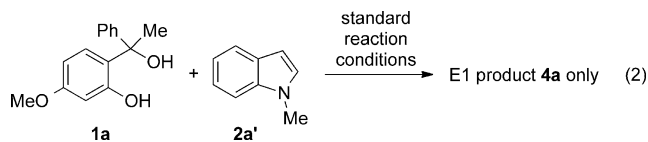
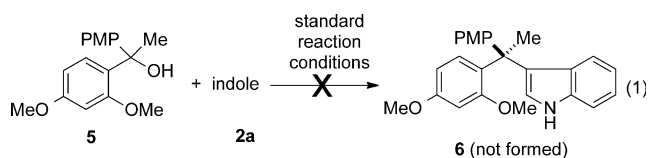


Scheme 2. Proposed mechanism.

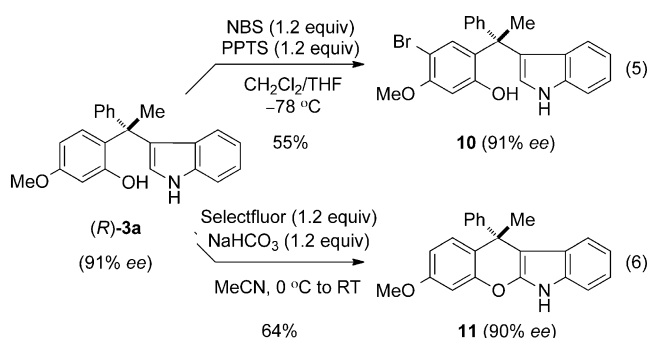
which is paired with the chiral phosphate anion. Subsequent indole nucleophilic attack delivers the observed product **3**. The structure **I** has a resonance form, **II**, which is represented as an acid-activated *o*-quinone methide. These structures can be viewed as two extreme forms of the real intermediate in terms of electron-density distribution. The efficient chiral induction, either by chiral phosphate through an ion-pair (in **I**) or hydrogen-bonding (in **II**), to form the all-carbon quaternary stereocenter is noteworthy.^[8–11]

To probe the reaction mechanism, we have done some control experiments. With the methyl ether **5**, none of the desired product **6** was observed, thus indicating the essential role of the free *o*-hydroxy group [Eq. (1); PMP = *p*-methyl-phenyl]. Next, *N*-methylindole (**2a'**) was subjected to the standard protocol, and the desired C–C bond formation was not observed. Instead, the E1 product **4a** was obtained [Eq. (2)]. We believe that the indole NH moiety provides a hydrogen-bonding interaction with the catalyst phosphoryl oxygen atom.^[12] Furthermore, we synthesized the β -mono-substituted *o*-quinone methide **7** and the corresponding

secondary alcohol **9**. They both reacted to form the desired product **8** with moderate enantioselectivity [Eqs. (3) and 4].



To demonstrate the product utility, we carried out some derivatizations. The product (*R*)-**3a** can undergo selective bromination in the presence of NBS and PPTS to form the aryl bromide **10** [Eq. (5); NBS = *N*-bromosuccinimide, PPTS = pyridinium *p*-toluenesulfonate]. Furthermore, promoted by Selectfluor, (*R*)-**3a** can cyclize to form the diaryl ether **11** [Eq. (6)]. The reaction may proceed by fluoroetherification with subsequent HF elimination. Such indole-containing products/derivatives bearing an all-carbon quaternary stereocenter are prevalent subunits in natural products and biologically active molecules.^[5f–h]



In summary, we have demonstrated an unprecedented catalytic asymmetric intermolecular process for the efficient formation of acyclic all-carbon quaternary stereocenters from racemic tertiary alcohols. The reaction features excellent stereocontrol and intermolecular C–C bond formation efficiency. The highly enantioenriched indole products bearing a quaternary stereocenter can be transformed into other

useful compounds. Preliminary control experiments provided insight into the reaction mechanism.

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- [1] a) K. Fuji, *Chem. Rev.* **1993**, 93, 2037–2066; b) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, 110, 402–415; *Angew. Chem. Int. Ed.* **1998**, 37, 388–401; c) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, 113, 4725–4732; *Angew. Chem. Int. Ed.* **2001**, 40, 4591–4597; d) J. Christoffers, A. Baro, *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim, **2005**.
- [2] a) J. P. Das, I. Marek, *Chem. Commun.* **2011**, 47, 4593–4623; b) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, 46, 7295–7306; c) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, 101, 5363–5367; d) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396; e) K. Hojoh, Y. Shido, H. Ohmiya, M. Sawamura, *Angew. Chem.* **2014**, 126, 5054–5058; *Angew. Chem. Int. Ed.* **2014**, 53, 4954–4958; f) I. Marek, Y. Minko, M. Pasco, T. Mejuch, N. Gilboa, H. Chechik, J. P. Das, *J. Am. Chem. Soc.* **2014**, 136, 2682–2694; g) L. Gao, B. C. Kang, D. H. Ryu, *J. Am. Chem. Soc.* **2013**, 135, 14556–14559; h) P. A. Evans, S. Oliver, J. Chae, *J. Am. Chem. Soc.* **2012**, 134, 19314–19317.
- [3] Current examples are limited to indol-3-yl carbocations, which were viewed as extended iminiums: a) C. Guo, J. Song, J.-Z. Huang, P.-H. Chen, S.-W. Luo, L.-Z. Gong, *Angew. Chem.* **2012**, 124, 1070–1074; *Angew. Chem. Int. Ed.* **2012**, 51, 1046–1050; b) L. Song, Q.-X. Guo, X.-C. Li, J. Tian, Y.-G. Peng, *Angew. Chem.* **2012**, 124, 1935–1938; *Angew. Chem. Int. Ed.* **2012**, 51, 1899–1902; c) J. Song, C. Guo, A. Adele, H. Yin, L.-Z. Gong, *Chem. Eur. J.* **2013**, 19, 3319–3323; d) M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem.* **2008**, 120, 603–606; *Angew. Chem. Int. Ed.* **2008**, 47, 593–596 (moderate enantioselectivity); e) W. Tan, B.-X. Du, X. Li, X. Zhu, F. Shi, S.-J. Tu, *J. Org. Chem.* **2014**, 79, 4635–4643.
- [4] For a review of nucleophilic substitutions to form tertiary, instead of quaternary stereocenters, see: a) A. Gualandi, P. G. Cozzi, *Synlett* **2013**, 281–296; for some representative examples, see: b) Q.-X. Guo, Y.-G. Peng, J.-W. Zhang, L. Song, Z. Feng, L.-Z. Gong, *Org. Lett.* **2009**, 11, 4620–4623; c) F.-L. Sun, M. Zeng, Q. Gu, S.-L. You, *Chem. Eur. J.* **2009**, 15, 8709–8712; d) F.-L. Sun, X.-J. Zheng, Q. Gu, Q.-L. He, S.-L. You, *Eur. J. Org. Chem.* **2010**, 47–50; e) M. Rueping, U. Uria, M.-Y. Lin, I. Atodiresi, *J. Am. Chem. Soc.* **2011**, 133, 3732–3735; f) D. Wilcke, E. Herdtweck, T. Bach, *Synlett* **2011**, 1235–1238; g) S.-G. Wang, L. Han, M. Zeng, F.-L. Sun, W. Zhang, S.-L. You, *Org. Biomol. Chem.* **2012**, 10, 3202–3209; h) M.-H. Zhuo, Y.-J. Jiang, Y.-S. Fan, Y. Gao, S. Liu, S. Zhang, *Org. Lett.* **2014**, 16, 1096–1099; i) P.-S. Wang, X.-L. Zhou, L.-Z. Gong, *Org. Lett.* **2014**, 16, 976–979.
- [5] For selected reviews on indoles in organic synthesis, see: a) E. Marqués-López, A. Díez-Martínez, P. Merino, R. P. Herrera, *Curr. Org. Chem.* **2009**, 13, 1585–1609; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, 105, 2873–2920; c) M. Shiri, *Chem. Rev.* **2012**, 112, 3508–3549; d) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, 121, 9786–9824; *Angew. Chem. Int. Ed.* **2009**, 48, 9608–9644; for reviews on indole-containing natural products and biologically active molecules, see: e) R. J. Sundberg, *Indoles*, Academic Press, London, **1996**; f) A. J. Kochanowska-Kar-

- amyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489–4497; g) M. Zeng, S.-L. You, *Synlett* **2010**, 1289–1301.
- [6] For recent reviews on chiral phosphoric acid catalysis, see: a) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999–1010; b) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; c) M. Terada, *Chem. Commun.* **2008**, 4097–4112; d) G. Adair, S. Mukherjee, B. List, *Aldrichimica Acta* **2008**, *41*, 31–39; e) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190–2201; f) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, *291*, 395–456; g) A. Zamfir, S. Schenker, M. Freund, S. B. Tsogoeva, *Org. Biomol. Chem.* **2010**, *8*, 5262–5276; h) M. Terada, *Synthesis* **2010**, 1929–1982; i) M. Rueping, R. M. Koenigs, I. Atodiresei, *Chem. Eur. J.* **2010**, *16*, 9350–9365; j) J. Yu, F. Shi, L. Gong, *Acc. Chem. Res.* **2011**, *44*, 1156–1171; k) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.* **2011**, *40*, 4539–4549; l) M. Rueping, W. Ieawsuwan, I. Atodiresei, *Angew. Chem.* **2011**, *123*, 6838–6853; *Angew. Chem. Int. Ed.* **2011**, *50*, 6706–6720; m) I. Čorić, S. Vellalath, S. Müller, X. Cheng, B. List, *Top. Organomet. Chem.* **2013**, *44*, 165–194.
- [7] Our effort in chiral acid catalysis: a) Z. Chen, B. Wang, Z. Wang, G. Zhu, J. Sun, *Angew. Chem.* **2013**, *125*, 2081–2085; *Angew. Chem. Int. Ed.* **2013**, *52*, 2027–2031; b) Z. Wang, Z. Chen, J. Sun, *Angew. Chem.* **2013**, *125*, 6817–6820; *Angew. Chem. Int. Ed.* **2013**, *52*, 6685–6688; c) Z. Chen, Z. Wang, J. Sun, *Chem. Eur. J.* **2013**, *19*, 8426–8430; d) Z. Wang, W. K. Law, J. Sun, *Org. Lett.* **2013**, *15*, 5964–5966; e) Z. Chen, J. Sun, *Angew. Chem.* **2013**, *125*, 13838–13841; *Angew. Chem. Int. Ed.* **2013**, *52*, 13593–13596.
- [8] Chiral anion induction for tertiary carbocations remains challenging. For some reviews: a) J. Lacour, D. Moraleda, *Chem. Commun.* **2009**, 7073–7089; b) J.-F. Brière, S. Oudeyer, V. Dalla, V. Levacher, *Chem. Soc. Rev.* **2012**, *41*, 1696–1707; c) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem.* **2012**, *4*, 603–614; d) M. Mahlau, B. List, *Angew. Chem.* **2013**, *125*, 540–556; *Angew. Chem. Int. Ed.* **2013**, *52*, 518–533; e) K. Brak, E. N. Jacobsen, *Angew. Chem.* **2013**, *125*, 558–588; *Angew. Chem. Int. Ed.* **2013**, *52*, 534–561.
- [9] For some examples of conjugate addition to β,β -disubstituted enones to generate all-carbon quaternary stereocenters, see: a) Y. Tanaka, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 8862–8863; b) K. Matoba, H. Kawai, T. Furukawa, A. Kusuda, E. Tokunaga, S. Nakamura, M. Shiro, N. Shibata, *Angew. Chem.* **2010**, *122*, 5898–5902; *Angew. Chem. Int. Ed.* **2010**, *49*, 5762–5766; c) P. Kwiatkowski, K. Dudziński, D. Łyżwa, *Org. Lett.* **2011**, *13*, 3624–3627; d) K. Akagawa, K. Kudo, *Angew. Chem.* **2012**, *124*, 12958–12961; *Angew. Chem. Int. Ed.* **2012**, *51*, 12786–12789; for some examples with β,β -disubstituted nitroalkenes, see: e) R. Kastl, H. Wennemers, *Angew. Chem.* **2013**, *125*, 7369–7373; *Angew. Chem. Int. Ed.* **2013**, *52*, 7228–7232; f) L.-A. Chen, X. Tang, J. Xi, W. Xu, L. Gong, E. Meggers, *Angew. Chem.* **2013**, *125*, 14271–14275; *Angew. Chem. Int. Ed.* **2013**, *52*, 14021–14025; g) J.-Q. Weng, Q.-M. Deng, L. Wu, K. Xu, H. Wu, R.-R. Liu, J.-R. Gao, Y.-X. Jia, *Org. Lett.* **2014**, *16*, 776–779; h) K. Mori, M. Wakazawa, T. Akiyama, *Chem. Sci.* **2014**, *5*, 1799–1803.
- [10] *o*-Quinone methides (*o*-QMs) are important species in organic synthesis. However, their catalytic asymmetric reactions are scarce. To our knowledge, catalytic asymmetric reactions of β,β -disubstituted *o*-QMs are unknown. For some reviews: a) R. W. Van De Water, T. R. R. Pettus, *Tetrahedron* **2002**, *58*, 5367–5405; b) T. P. Pathak, M. S. Sigman, *J. Org. Chem.* **2011**, *76*, 9210–9215; c) N. J. Willis, C. D. Bray, *Chem. Eur. J.* **2012**, *18*, 9160–9173.
- [11] a) No kinetic resolution of the starting material **1a** was observed, that is, at partial conversion the starting alcohol remained racemic. b) With the enantioenriched **1a** (97% *ee*) as the starting material, the product **3a** was formed in comparable enantiomeric excess (90% *ee*). At partial conversion, the *ee* values of the starting **1a** and the product **3a** both remained essentially constant, thus suggesting an irreversible first step.
- [12] For examples, see: a) Y.-X. Jia, J. Zhong, S.-F. Zhu, C.-M. Zhang, Q.-L. Zhou, *Angew. Chem.* **2007**, *119*, 5661–5663; *Angew. Chem. Int. Ed.* **2007**, *46*, 5565–5567; b) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2008**, *120*, 4080–4082; *Angew. Chem. Int. Ed.* **2008**, *47*, 4016–4018; for a theoretical study, see: c) L. Simón, J. M. Goodman, *J. Org. Chem.* **2010**, *75*, 589–597.