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Titanocene-Catalyzed Multicomponent Coupling Approach to Diarylethynyl Methanes

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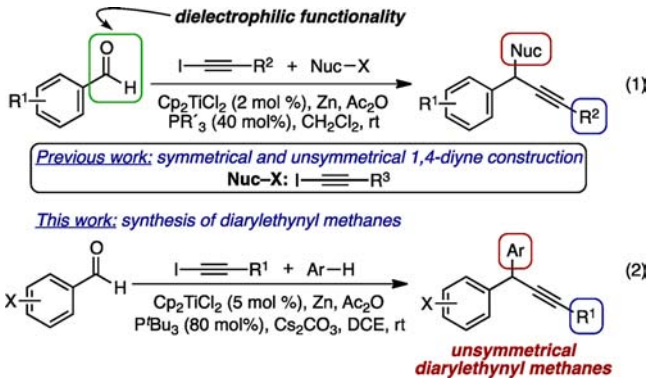
Supporting Information

ABSTRACT: A titanocene-catalyzed multicomponent coupling to provide diarylethynyl methanes is described. By combining the multifunctionality of Cp_2TiCl_2 with the traceless dielectrophilicity of aryl aldehydes, all-carbon tertiary centers are obtained in 55−99% yield.

The addition of carbon nucleophiles to carbonyl derivatives remains one of the foremost strategies to construct C−C bonds.[1] However, the synthesis of highly substituted all-carbon centers from a carbonyl precursor typically requires multiple synthetic operations, including a deoxygenation step that often leads to issues of chemoselectivity.[2] To address these obstacles that limit the utility of this ubiquitous functional group, we sought a protocol that enables the addition of two distinct carbon nucleophiles employing a single transition metal catalyst in a synthetically efficient manner (eq 1). Based on our previous



work toward 1,4-diynes,[3] we speculated that employing aryl nucleophiles in a titanocene-catalyzed multicomponent coupling would enable the direct assembly of unsymmetrical diarylethynyl methanes (eq 2).[4]

The diaryl-substituted tertiary carbon is a prevalent structural motif in nature, as exemplified by ampelopsin D (**1**),[5] fischerisin A (**2**),[6] and calyxins B (**3**) and C (**4**)[7] (Figure 1). The intriguing biological properties associated with these natural products make this architectural subunit a worthy synthetic target.[8] A one-pot diarylethynyl methane synthesis directly from aldehydes offers the opportunity for a flexible and modular synthesis of this substructure. Additionally, incorporation of the alkyne unit provides a versatile functional handle for further secondary transformations. Herein, we report a highly convergent assembly of tertiary all-carbon centers that exploits the redox and Lewis acidic properties

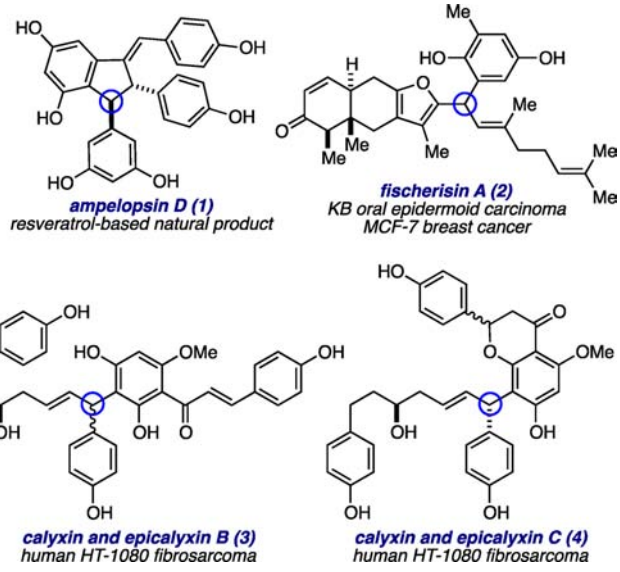
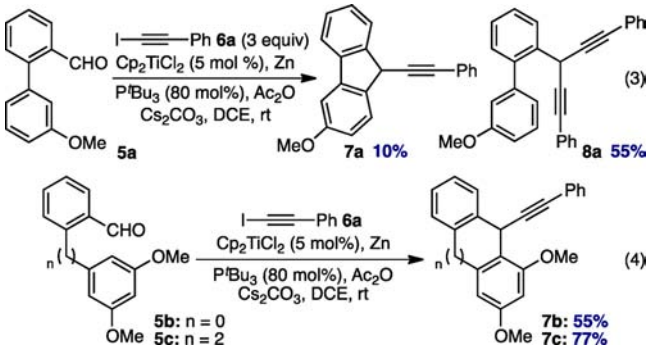


Figure 1. Diarylmethane-containing natural products.

of low-valent titanocene[9] using an aryl aldehyde as a traceless dielectrophilic functionality.

We began our study by evaluating the titanocene-catalyzed alkynylation/arylation sequence using methoxy-substituted biphenyl aldehyde **5a** and iodoalkyne **6a** (eq 3). By treating **5a** and **6a**



with Cp_2TiCl_2 (5 mol%), $^tBu_3P$, and zinc dust in the presence of Ac_2O and Cs_2CO_3, we obtained fluorene **7a** in 10% yield along with a substantial amount of diyne **8a**.[3] Employing the more electron-rich biaryl aldehyde **5b** effectively suppressed competitive 1,4-diyne formation, yielding fluorene **7b** in 55%

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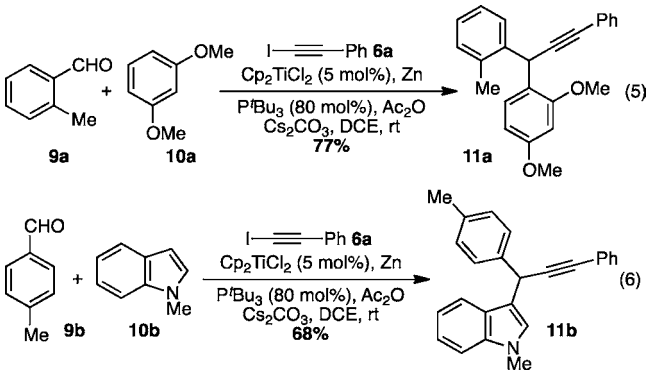
(eq 4). Furthermore, exposing diarylethane **5c** to identical conditions provided the seven-membered ring adduct **7c** in 77% yield.

Emboldened by our initial success in constructing cyclic diarylethynyl methanes, we turned our attention toward examining the feasibility of an intermolecular multicomponent coupling. Gratifyingly, subjection of aldehyde **9a**, arene **10a**, and iodoalkyne **6a** to our titanocene-catalyzed coupling conditions gave diarylethynyl methane **11a** in 77% yield (eq 5). Extending this initial



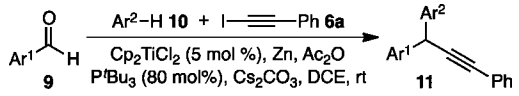
finding to heteroaryl nucleophiles led to the successful coupling with *N*-methylindole (**10b**), aldehyde **9b**, and **6a** to provide diarylethynyl methane **11b**, resulting from exclusive indole C3 alkylation, in 68% yield (eq 6). Given the pharmaceutical significance of indole alkaloids,[10] and the synthetic versatility of alkynes, this method constitutes a powerful tool for the synthesis of functionalized indoles.[11]

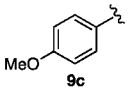
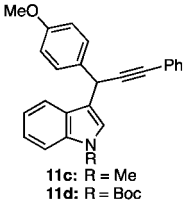
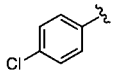
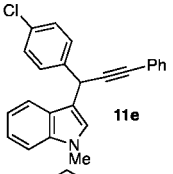
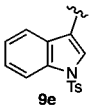
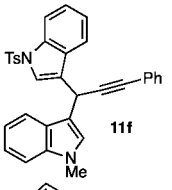
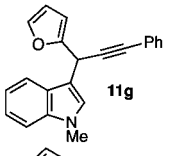
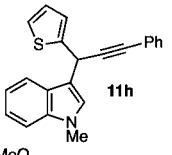
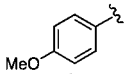
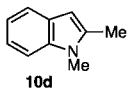
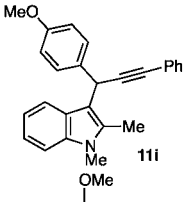
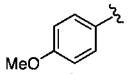
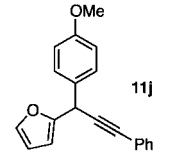
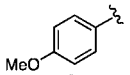
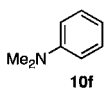
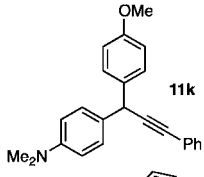
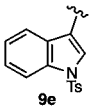
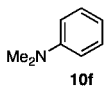
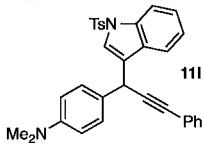
Upon examination, we discovered that the titanocene-catalyzed multicomponent coupling of aryl aldehydes **9** and arenes **10** with **6a** proved general for a wide array of functionally diverse substrates (Table 1). Alkylation of electron-rich and electron-poor aldehydes **9c** and **9d** with indole **10b** provided the expected diarylethynyl methanes in good yields (entries 1 and 2). Additionally, the presence of an *N*-acyl protecting group on indole **10c** did not adversely effect the formation of **11e** (entry 1). The coupling of aldehydes bearing an indole (**9e**), furyl (**9f**), or thiophenyl (**9g**) heteroaryl ring with indole **10b** and **6a** yielded the unsymmetrical diarylethynyl methanes **11f–h** respectively in 68–71% yields (entries 3–5). Consistent with our initial findings, electron-rich aryl rings proved superior to their neutral and electron-deficient counterparts. The addition of C2-substituted indole **10d** and **6a** to aldehyde **9c** provided adduct **11i** in 80% yield (entry 6). Coupling of aldehyde **9c** and **6a** with either furan **10e** or aniline **10f** provided adducts **11j** and **11k** in excellent yields (entries 7 and 8). Finally, aniline **10f** also proved effective in the coupling of 3-formylindole **9e** and **6a** to yield **11l** (entry 9).

The titanocene-catalyzed coupling also proved general for a range of iodoalkynes **6** in the alkylation of aldehyde **9c** and indole **10b** (Table 2). Electron-rich and electron-poor aryl iodoalkynes **6b–d** provided the corresponding diarylethynyl methanes **11m–o** in good yields (entries 1–3). Aliphatic alkynyl iodides **6e** and **6f** gave propargyl indoles **11p** and **11q** in 80% and 58% yield, respectively (entries 4 and 5). Silyl iodoalkyne **6g**, an effective acetylene surrogate, coupled efficiently with **9c** and **10b** to yield diarylethynyl methane **11r** (entry 6). It is noteworthy that, although both iodoalkyne and Ar–H nucleophiles are present throughout the reaction, the formation of 1,4-diynes or triarylmethanes was not observed.

In an effort to evaluate a more structurally complex component, we chose iodoalkyne **6h**, corresponding to the C1–C6 fragment of the acyclic calyxin diarylheptanoids illustrated in Figure 1 (eq 7). Construction of enantioenriched **6h** was

Table 1. Aromatic Dielectrophiles and Nucleophiles[a]



Entry	Ar^1	Ar^2	Product[b]	
1				**11c:** 90% **11d:** 63%
2				63%
3				69%
4				68%
5				71%
6				80%
7				98%
8				81%
9				68%

[a]Conditions: 0.2 mmol of **9**, 0.4 mmol of **10**, 0.6 mmol of **6a**, Cp_2TiCl_2, $^tBu_3P$, 0.6 mmol of zinc dust, 0.2 mmol of Ac_2O, 0.2 mmol of Cs_2CO_3 in DCE (0.1 M). [b]Isolated yields.

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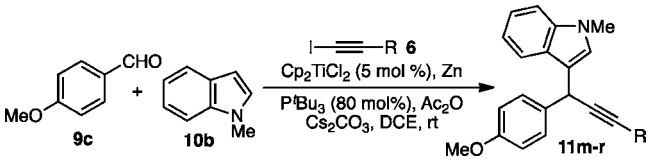
Table 2. Iodoalkyne Component[a]



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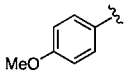
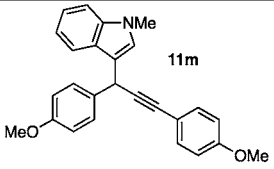
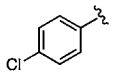
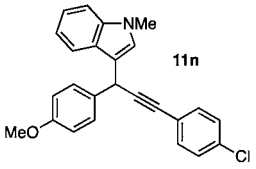
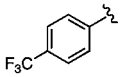
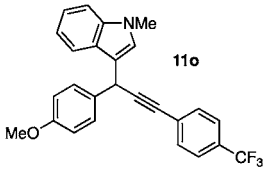
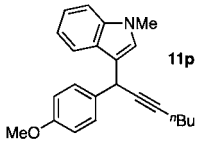
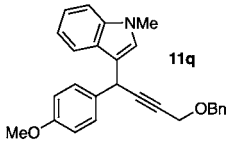
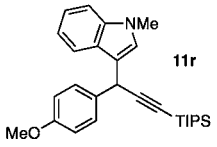
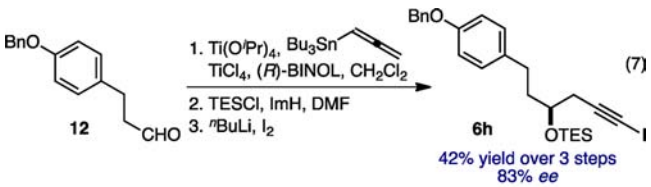
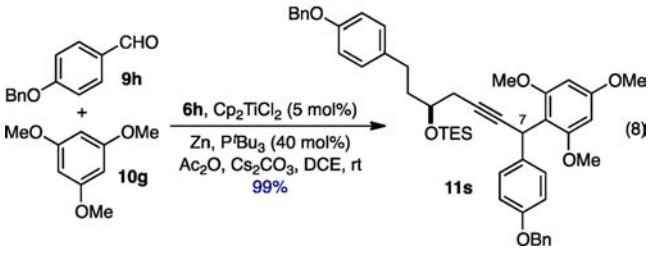
1	 6b	 11m	83%
2	 6c	 11n	83%
3	 6d	 11o	80%
4	^{n}Bu 6e	 11p	80%
5	$BnOCH_2$ 6f	 11q	58%
6	TIPS 6g	 11r	67%

[a]Conditions: same as Table 1. [b]Isolated yields.

accomplished in three steps from known aldehyde **12**[12] using a titanium-catalyzed asymmetric propargylation.[13] Treatment of **6h**, aldehyde **9h**, and arene **10g** with Cp_2TiCl_2 (5 mol%), $^tBu_3P$, Zn, Cs_2CO_3, and Ac_2O provided diarylethynyl methane **11s** in 99% overall yield as a 1:1 mixture of C7 epimers (eq 8). Interestingly, 40 mol% of P^tBu_3 was required for full conversion, whereas 80 mol% led to arrest at the intermediate propargylic acetate. Notably, unreacted arene and the terminal alkyne, resulting from reduction of iodoalkyne **6h**, were recovered quantitatively.

Consistent with our previous work involving the titanocene-catalyzed metalation of C–X bonds,[3,9d,14] there appears to be a synergistic effect of Cp_2TiCl_2, Zn^0, and $^tBu_3P$ in formation of the first C–C bond resulting from acetylide addition to aldehyde **9**.[9f,15] This is supported by the observation that, in the absence of Cp_2TiCl_2, Zn^0, or Ac_2O after prolonged reaction times (>48 h), only starting aldehyde or propargylic alcohol/acetate was obtained. In contrast to the redox assembly of 1,4-diynes,[3] the second C–C bond-forming event en route to diarylethynyl methanes likely occurs via a Lewis acid-catalyzed propargylic arylation involving either an oxophilic titanocene





complex or Zn^{II} salt.[16] However, a single electron transfer redox process involving an $S_{RN}1$ aromatic substitution catalyzed by $Cp_2Ti^{III}Cl$ cannot be excluded at this time.[9e] Additional evidence for a propargylic cation or radical intermediate was obtained by treating cinnamaldehyde with indole **10b** and iodoalkyne **6a** under the reaction conditions to yield a 1:1 mixture of allylically transposed arylation products. Although the role of phosphine is unclear at this stage, it may serve to stabilize low-valent titanocene intermediates, while increasing the reactivity of metal acetylides through an unusual P–Zn ligation.[17]

In summary, we have developed a versatile approach toward diarylethynyl methanes by harnessing the multifunctional attributes of low valent titanocene. This multicomponent coupling permits a high degree of modularity and convergency in the rapid assembly of complex targets around the construction of a single all-carbon substituted tertiary center. The application of this method to the synthesis of biologically active natural products, and studies aimed at elucidating the mechanism of C–C bond formation, are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(1) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B: Reaction and Synthesis*, 5th ed.; Springer: New York, 2007.

(2) (a) Seebach, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 96. (b) Xi, Z.; Song, Q.; Chen, J.; Guan, H.; Li, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1913. (c) Reetz, M. T.; Westermann, J. *J. Org. Chem.* **1983**, *48*, 254. (d) Reetz, M. T.; Westermann, J.; Steinbach, R. *Angew. Chem., Int. Ed.* **1980**, *19*, 900.

(3) Campos, C. A.; Gianino, J. B.; Pinkerton, D. M.; Ashfeld, B. L. *Org. Lett.* **2011**, *13*, 5680.
(4) (a) Xiang, S.-K.; Zhang, L.-H.; Jiao, N. *Chem. Commun.* **2009**, 6487. (b) Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1414. (c) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 13590.
(5) (a) Snyder, S. A.; Zografos, A. L.; Lin, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 8186. (b) Takaya, Y.; Yan, K.-X.; Terashima, K.; Ito, J.; Niwa, M. *Tetrahedron* **2002**, *58*, 7259.
(6) Xie, W.-D.; Li, X.; Weng, C.-W.; Liu, S.-S.; Row, K. H. *Chem. Pharm. Bull.* **2011**, *59*, 511.
(7) (a) Tezuka, Y.; Ali, M. S.; Banskota, A. H.; Kadota, S. *Tetrahedron Lett.* **2000**, *41*, 5903. (b) Gewali, M. B.; Tezuka, Y.; Banskota, A. H.; Ali, M. S.; Saiki, I.; Dong, H.; Kadota, S. *Org. Lett.* **1999**, *1*, 1733. (c) Prasain, J. K.; Tezuka, Y.; Li, J.-X.; Tanaka, K.; Basnet, P.; Dong, H.; Namba, T.; Kadota, S. *J. Chem. Res.* **1998**, 22. (d) Prasain, J. K.; Li, J.-X.; Tezuka, Y.; Tanaka, K.; Basnet, P.; Dong, H.; Namba, T.; Kadota, S. *J. Nat. Prod.* **1998**, *61*, 212. (e) Kadota, S.; Dong, Hui; Basnet, P.; Prasain, J. K.; Xu, G.-J.; Namba, T. *Chem. Pharm. Bull.* **1994**, *42*, 2647.
(8) (a) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389. (b) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096. (c) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9331. For synthetic approaches to the calyxins, see: (d) Bunt, A. J.; Bailey, C. D.; Cons, B. D.; Edwards, S. J.; Elsworth, J. D.; Pheko, T.; Willis, C. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 3901. (e) Cakir, S. P.; Stokes, S.; Sygula, A.; Mead, K. T. *J. Org. Chem.* **2009**, *74*, 7529. (f) Tian, X.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 4955. (g) Washio, T.; Nambu, H.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2007**, *18*, 2606. (h) Cakir, S. P.; Mead, K. T. *Tetrahedron Lett.* **2006**, *47*, 2451. (i) Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176.
(9) (a) Gansäuer, A.; Behlendorf, M.; von Laufenberg, D.; Fleckhaus, A.; Kube, C.; Sadasivam, D. V.; Flowers, R. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4739. (b) Kosal, A. D.; Ashfeld, B. L. *Org. Lett.* **2010**, *12*, 44. (c) Justicia, J.; Sancho-Sanz, I.; Álvarez-Manzaneda, E.; Oltra, J. E.; Cuerva, J. M. *Adv. Synth. Catal.* **2009**, *351*, 2295. (d) Fleury, L. M.; Ashfeld, B. L. *Org. Lett.* **2009**, *11*, 5670. (e) Yang, F.; Zhao, G.; Ding, Y.; Zhao, Z.; Zheng, Y. *Tetrahedron Lett.* **2002**, *43*, 1289. (f) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849. (g) Dang, Y.; Geise, H. J. *J. Organomet. Chem.* **1991**, *405*, 1. (h) McMurry, J. E. *Acc. Chem. Res.* **1974**, *7*, 281.
(10) (a) Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocycl. Chem.* **2010**, *47*, 491. (b) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489. (c) Frederich, M.; Tits, M.; Angenot, L. *Trans. R. Soc. Trop. Med. H* **2008**, *102*, 11. (d) Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442.
(11) (a) Sanz, R.; Miguel, D.; Gohain, M.; Garcia-Garcia, P.; Fernandez-Rodriguez, M. A.; González-Pérez, A.; Nieto-Faza, O.; de Lera, Á. R.; Rodriguez, F. *Chem. Eur. J.* **2010**, *16*, 9818. (b) Facoetti, D.; Abbiati, G.; Rossi, E. *Eur. J. Org. Chem.* **2009**, *2009*, 2872. (c) Sanz, R.; Miguel, D.; Rodriguez, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7354.
(12) Boulard, L.; BouzBouz, S.; Cossy, J.; Franck, X.; Figadère, B. *Tetrahedron Lett.* **2004**, *45*, 6603.
(13) (a) Usanov, D. L.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, *133*, 1286. (b) Hanawa, H.; Uraguchi, D.; Konishi, S.; Hashimoto, T.; Maruoka, K. *Chem. Eur. J.* **2003**, *9*, 4405.
(14) Fleury, L. M.; Ashfeld, B. L. *Tetrahedron Lett.* **2010**, *51*, 2427.
(15) (a) Ogata, A.; Nemoto, M.; Kobayashi, K.; Tsubouchi, A.; Takeda, T. *Chem. Eur. J.* **2007**, *13*, 1320. (b) Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Muck-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359. (c) Gansäuer, A.; Narayan, S. *Adv. Synth. Catal.* **2002**, *344*, 465.
(16) (a) Rubenbauer, P.; Herdtweck, E.; Strassner, T.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 10106. (b) Liu, Z.; Liu, L.; Shafiq, Z.; Wu, Y.-C.; Wang, D.; Chen, Y.-J. *Synthesis* **2007**, 1961. (c) Netz, A.; Polborn, K.; Müller, T. J. J. *J. Am. Chem. Soc.* **2001**, *123*, 3441.
(17) Wilson, E. E.; Oliver, A. G.; Hughes, R. P.; Ashfeld, B. L. *Organometallics* **2011**, *30*, 5214.