Tetrahedron Letters 55 (2014) 5025–5028

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Titanocene-catalyzed metallation of propargylic acetates in homopropargyl alcohol synthesis

Jennifer L. Meloche, Peter T. Vednor, Joseph B. Gianino, Allen G. Oliver, Brandon L. Ashfeld *

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN 46637, United States

ARTICLE INFO

Article history:
Received 15 April 2014
Revised 1 July 2014
Accepted 3 July 2014
Available online 17 July 2014

Keywords:
Titanocene-catalyzed
Propargylic acetates
Homopropargyl alcohols
Metallation/carbonyl addition

ABSTRACT

The titanium-catalyzed metallation and subsequent carbonyl addition of propargylic acetates enable the direct formation of homopropargylic alcohols in good yields. The corresponding products were obtained as single regioisomers without the corresponding allene adducts observed.

Despite the growing number of uses for homopropargyl alcohols in π-Lewis acid mediated rearrangements,[1] the addition of propargylic or allenic organometallics to carbonyls has received less attention than the closely related allylation.[2] The use of main group organometallics[3] often yields regioisomeric mixtures of homopropargylic and allenic alcohols, and the metallation conditions are typically incompatible with sensitive functionality.[4] In contrast, the *in situ* formation of propargyl zinc,[3d,5] chromium,[6] zirconium,[7] and titanium[8] complexes can avoid issues of chemoselectivity, while regioselectivity is highly dependent on the substitution pattern of the propargylic substrate.[8f,9] Herein, we have developed a complementary protocol that allows for the mild generation of a propargyl organometallic, that proceeds with a high degree of regioselectivity in the carbonyl addition event (Fig. 1a). Our protocol utilizes a combination of catalytic titanocene and stoichiometric zinc dust to facilitate the metallation of readily prepared propargylic acetates.[2a,h,10]

We were encouraged by reports from Ding[11] and Cuerva[12] illustrating the stoichiometric titanation of propargylic acetates and titanocene-catalyzed carbonyl addition of propargyl halides, respectively, to explore the titanocene-catalyzed metallation-carbonyl addition sequence involving propargylic acetates and aldehydes. We speculated that catalytic Cp_2TiCl_2 and zinc dust would facilitate the direct metallation of propargylic acetates **1** in the presence of aldehyde **2** to regioselectivity generate the desired alcohol adduct **3** (Fig. 1b).[13]

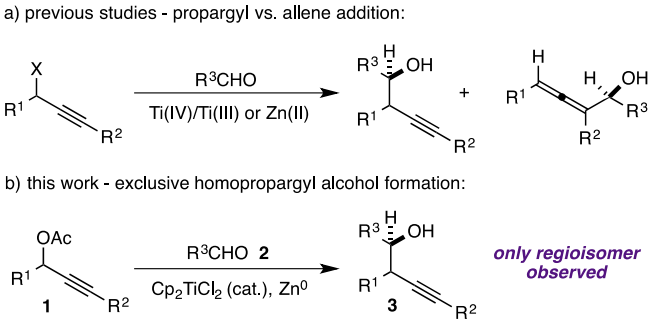


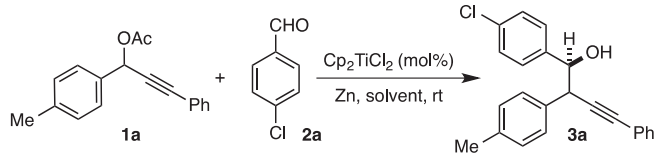
Figure 1. Propargyl metal addition to aldehydes.

Inspired by our previous work on titanocene-catalyzed catalyzed metallations and multicomponent couplings,[2a,h,13,14] we sought to establish the use of propargylic acetate **1a** as a viable organometallic precursor in the synthesis of alcohol **3a** (Table 1). In general, we discovered that Zn dust (2 equiv) was superior to both Mg turnings and Mn powder as the terminal reductant, and that the amount of titanocene proved crucial to achieving a good yield of **3a**. For example, while 5 mol % Cp_2TiCl_2 and Zn dust in CH_2Cl_2 gave homopropargylic alcohol **3a** in 12% yield, increasing the catalyst loading to 10 mol % showed a dramatic increase in yield to 57% (entries 1 and 2). Ultimately, 20 mol % of Cp_2TiCl_2 led to 69% yield of **3a** (entry 4). While too much catalyst proved detrimental, titanocene was necessary to achieve any product formation as the absence of the catalyst led to complete recovery of starting material even after prolonged reaction times (>48 h, entry

* Corresponding author.
E-mail address: bashfeld@nd.edu (B.L. Ashfeld).

http://dx.doi.org/10.1016/j.tetlet.2014.07.029
0040-4039/

Table 1
Optimization of reaction conditions[a]



Entry	Cp_2TiCl_2 (mol %)	Solvent	Yield[b] (%)
1	5	CH_2Cl_2	12[c]
2	10	CH_2Cl_2	57
3	20	CH_2Cl_2	69
4	25	CH_2Cl_2	52[c]
5	0	CH_2Cl_2	—
6	20	DCE	21
7	20	THF	—

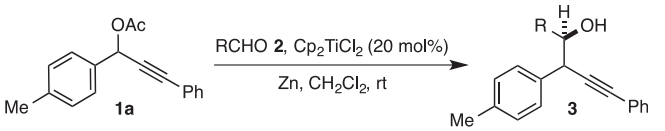
[a] Reaction conditions: **1a** (0.19 mmol), **2a** (0.38 mmol), Cp_2TiCl_2, and Zn (0.38 mmol), rt, 48 h.
[b] Isolated yields with an *anti*/*syn* = 1:1 determined by either 500 MHz ^{1}H NMR or HPLC, see Supporting information for details.
[c] Yields determined by 500 MHz ^{1}H NMR.

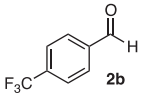
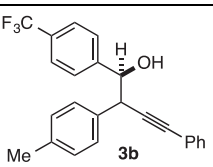
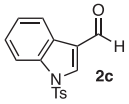
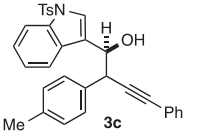
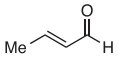
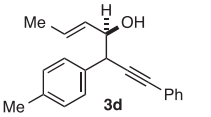
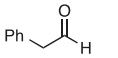
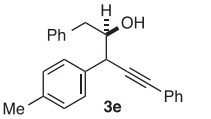
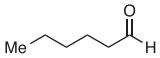
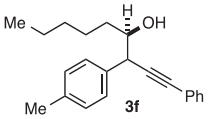
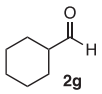
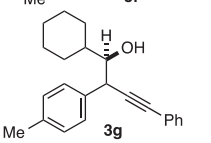
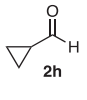
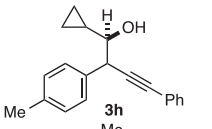
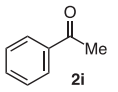
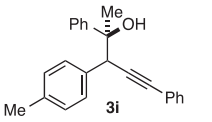
6). In each experiment depicted in Table 1, alcohol **3a** was obtained as a 1:1 mixture of *anti*/*syn* diastereomers across a broad spectrum of reaction temperatures (0 °C–80 °C).

With optimized conditions in hand, we turned our attention toward evaluating the structural variability of aldehyde **2** in the formation of alcohol **3**. In general, good yields of the corresponding homopropargyl alcohols were obtained upon treatment of propargyl acetate **1a** and a variety of aldehydes **2** with Cp_2TiCl_2 (20 mol %) and Zn dust (Table 1). Aryl aldehydes **2b** and **2c** gave decent yields of alcohols **3b** and **3c** (entries 1 and 2). It should be noted that electron rich aryl aldehydes proceeded in lower yields than the more electron deficient counterparts (e.g., *p*-$MeOC_6H_4CHO$–25%). α,β-Unsaturated aldehyde **2d** underwent exclusive 1,2-addition to provide the corresponding allylic alcohol **3d** in 55% yield (entry 3). Aliphatic aldehydes also proved viable in providing the corresponding alcohols in decent yields along with improved diastereoselectivities. Phenyl acetaldehyde (**2e**) and hexanal (**2f**) gave alcohols **3e** and **3f** in good yields and 1.6:1 and 2:1 dr, respectively, (entries 4 and 5). In contrast, carbocycle-substituted aldehydes, **2g** and **2h** underwent propargylation to give homopropargylic alcohols **3g** and **3h** in good yields and further improved diastereoselectivities (entries 6 and 7). Diastereomeric ratios are not enhanced when performed at lower temperatures, and inferior yields were observed. While ketones proved viable, the corresponding alcohols were formed in diminished yields. For example, acetophenone (**2i**) yielded alcohol **3i** in 30% yield and with a dr = 1.2:1 (entry 8).

We next turned our attention toward evaluating the functional group flexibility on propargyl acetate **1** in the coupling to aldehyde **2a** (Table 3). In contrast to the stoichiometric Cp_2Ti^{II}-mediated propargylation,[11c] aliphatic substrates were unreactive under this catalytic protocol. Neutral acetate **1b** and acetates **1c** and **1d** bearing electron rich aryl groups at R^2 gave alcohols **4a**, **4b**, and **4c** in comparable yields (entries 2 and 3). However, acetates with strong electron-withdrawing aryl groups at R^2 (e.g., *p*-O_2N-C_6H_4, *p*-Cl-C_6H_4, *p*-MeO_2C-C_6H_4) gave only trace quantities (<5%) of the expected product. Allyl acetate **1e** was sufficiently activated to facilitate metallation to give alcohol **4d** in 35% yield (entry 4). Electron rich aryl substitution on the alkyne in acetate **1f** gave alcohol **4e** in modest yield, while the corresponding electron poor aryl derivatives failed to undergo metallation (entry 5). Alkyl substitution on the alkyne proved beneficial, providing alcohols **4f** in 49% yield and **4g** in 60% yield (entry 6 and 7). In general, the metallation event proved highly dependent on the propargylic C–O bond strength given the mild reductants Cp_2TiCl_2 (cat.) and Zn dust employed.

Table 2
Carbonyl electrophile structural variability[a]

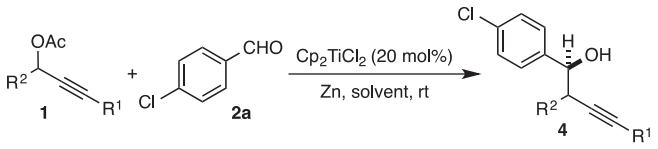


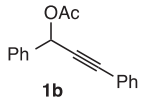
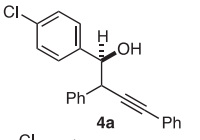
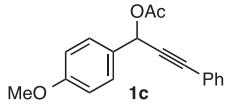
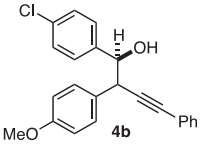
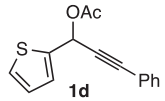
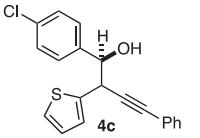
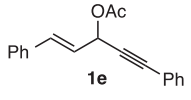
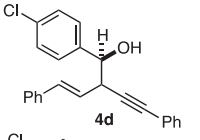
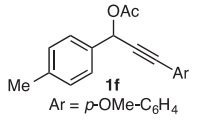
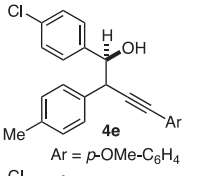
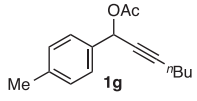
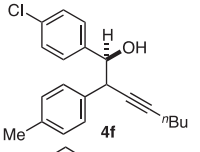
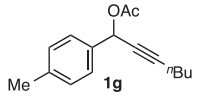
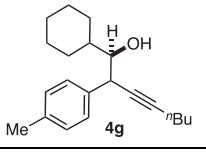
Entry	2	3	Yield[b,c] (%)
1			74 dr = 1:1
2			40 dr = 1:1
3			55 dr = 1.2:1
4			48 dr = 1.6:1
5			60 dr = 2:1
6			53 dr = 8:1
7			68 dr = 2.4:1
8			30 dr = 1.2:1

[a] Reaction conditions: **1** (0.19 mmol), **2** (0.38 mmol), Cp_2TiCl_2 (20 mol %), and Zn (0.38 mmol) in CH_2Cl_2 (0.25 M), rt, 48 h.
[b] Isolated yields.
[c] Ratios determined by either 500 MHz ^{1}H NMR or HPLC, see Supporting information for details.

In previous studies we reported that the addition of substoichiometric titanocene facilitated the formation of organozinc reagents directly from the corresponding halides.[2a,13] While allylic acetates proved unreactive, our subsequent work on a titanocene-catalyzed multicomponent coupling for the construction of tertiary all-carbon centers yielded evidence to suggest the intermediacy of a propargylic metal species.[14] To gain a better understanding we examined in more detail the conversions of **1a** and **2a** to alcohol **3a**. The absence of Cp_2TiCl_2 or Zn dust resulted in near quantitative recovery of the starting acetate **1a**. Using a stoichiometric amount of Cp_2TiCl or Cp_2TiCl_2 without Zn dust also gave ≤5% of the homopropargyl alcohol **3a**. These results suggest that neither titanocene nor Zn^0 are capable of independently facilitating both the metallation and carbonyl addition steps. Additionally, replacing Cp_2TiCl_2 with BF_3.OEt2 failed to provide

Table 3
Propargylic acetate functional group tolerance[a]



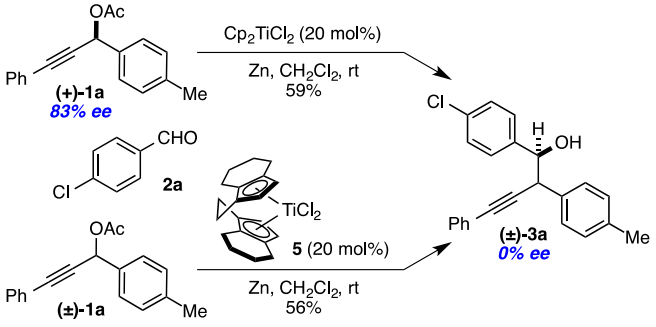
Entry	1	4	Yield[b] (%)
1			20
2			27
3			26
4			35
5	 Ar = *p*-OMe-C_6H_4	 Ar = *p*-OMe-C_6H_4	25
6[c]			49
7			60

[a] Reaction conditions: **1** (0.19 mmol), **2** (0.38 mmol), Cp_2TiCl_2 (20 mol %),and Zn (0.38 mmol) in CH_2Cl_2 (0.25 M), rt, 48 h.
[b] Isolated yields with an *anti*/*syn* = 1:1.
[c] *Anti*/*syn* = 1.7:1 determined by 500 MHz ^{1}H NMR.

homopropargylic alcohol **3a** suggesting that titanocene is likely not acting as a Lewis acid, and that both titanocene and zinc are involved in the metallation event.[2a,14d,15]

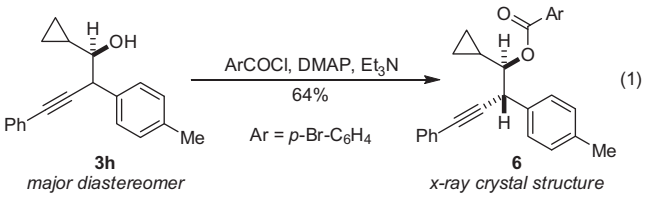
Further mechanistic insight was obtained by evaluating the stereochemical outcome of the metallation/carbonyl addition events. Addition of enantioenriched acetate (+)-**1a**[16] to aldehyde **2a** gave homopropargyl alcohol (±)-**3a** as a racemic mixture in 1:1 diastereoselectivity indicating the intermediacy of the configurationally unstable propargyl organometallic species (Scheme 1).[11b,14d,17] Additionally, treatment of racemic acetate **1a** using the chiral titanocene catalyst **5** failed to provide the corresponding alcohol **3a** with any appreciable enantioinduction or diastereoselectivity.

The relative configuration of the major diastereomer obtained in the carbonyl additions depicted in Table 2 was determined by X-ray crystallography. Isolation of the major **3h** diastereomer followed by acylation with *p*-bromobenzoyl chloride yielded



Scheme 1. Stereochemical consequence.

benzoate **6** as a fine, white solid (Eq. 1). Recrystallization and X-ray crystallography confirmed that the *anti* stereoisomer depicted was indeed the major product. While not definitive, it is reasonable to assume that the major diastereomers in Table 2 also bear an *anti* orientation.



(1)

Similar to a proposal by Yamamoto and coworkers, the C–C bond forming event likely proceeds through one of two possible closed transition states (Fig. 2).[9c] Formation of the *anti* diastereomer via **TS1** should be favored over **TS2** due to the minimization of eclipsing interactions between Ar and R on the allenyl metal complex and aldehyde, respectively. Given the increased acidity of the tertiary proton at the newly formed propargylic/benzylic center, we speculated that the diastereoselectivity observed resulted from epimerization of the tertiary center during the reaction. However, when a single diastereomer of **3a** was subjected to the reaction conditions, no epimerization was observed, which would indicate that the diastereomeric ratios are due to a kinetic preference for **TS1**.

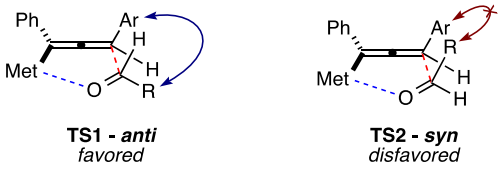


Figure 2. Rationalization of diastereoselectivity.

The requirement that both titanocene and zinc be present to provide the reactivity observed indicates a synergistic effect in the formation of an allenyl organometallic necessary to produce the observed propargylic alcohol. One possible mechanism that is consistent with our previous work on titanocene-catalyzed metallations,[13] involves an initial reductive transmetallation from a mixture of propargylic/allenyl titanocene species to give an allenyl zinc(II) organozinc[5a] that undergoes carbonyl addition through a closed transition state. The propargylation event then occurs regioselectivity with *anti* stereoselectivity that appears dependent on aldehyde steric approach control.[18] However, an alternative mechanism that includes $Cp_2(Cl)Ti–R$ as the intermediate involved in the C–C bond formation cannot be ruled out.[8f,9c]

In conclusion, we have established a convenient method for the metallation and carbonyl addition of propargylic acetates to give homopropargylic alcohols with complete regiocontrol. Although identification of the organometallic reagent directly involved in the C–C bond forming event is still under investigation, the reactivity observed suggests a cooperative effect between Cp_2TiCl_2 and Zn dust. Additional mechanistic studies are underway and will be reported in due course.

Acknowledgments

We thank the Walther Cancer Foundation and the University of Notre Dame for funding.

Supplementary data

Supplementary data (experimental procedures and compound characterizations) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.07.029.

References and notes

1. (a) Urabe, F.; Miyamoto, S.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2014**, *16*, 1004; (b) Shu, C.; Liu, M.-Q.; Sun, Y.-Z.; Ye, L.-W. *Org. Lett.* **2012**, *14*, 4958; (c) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657; (d) Camelio, A. M.; Barton, T.; Guo, F.; Shaw, T.; Siegel, D. *Org. Lett.* **2011**, *13*, 1517; (e) Allegretti, P. A.; Ferreira, E. M. *Org. Lett.* **2011**, *13*, 5924; (f) Weibel, J.-M.; Blanc, A.; Pale, P. *Chem. Rev.* **2008**, *108*, 3149; (g) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326; (h) Dai, L.-Z.; Shi, M. *Chem. Eur. J.* **2008**, *14*, 7011; (i) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266; (j) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095.
2. (a) Fleury, L. M.; Ashfeld, B. L. *Org. Lett.* **2009**, *11*, 5670; (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340; (c) Hall, D. *Synlett* **2007**, 1644; (d) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732; (e) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763; (f) Marshall, J. A. *Chem. Rev* **2000**, *100*, 3163; Yamamoto, H.; Trost, B.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991. vol. 2, 81; (h) Fleury, L. M.; Ashfeld, B. L. *Tetrahedron Lett.* **2010**, *51*, 2427.
3. (a) Chen, M.; Roush, W. R. *J. Am. Chem. Soc.* **2012**, *134*, 10947; (b) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, *117*, 6392; (c) Corey, E. J.; Yu, C. M.; Lee, D. H. *J. Am. Chem. Soc.* **1990**, *112*, 878; (d) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 5198; (e) Hahn, G.; Zweifel, G. *Synthesis* **1983**, *1983*, 883; (f) Daniels, R. G.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 1579.
4. Knoess, H. P.; Furlong, M. T.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1991**, *56*, 5974.
5. (a) Fandrick, D. R.; Saha, J.; Fandrick, K. R.; Sanyal, S.; Ogikubo, J.; Lee, H.; Roschangar, F.; Song, J. J.; Senanayake, C. H. *Org. Lett.* **2011**, *13*, 5616; (b) Yadav, J. S.; Reddy, B. V. S.; Chandrakanth, D.; Prashant, B. *Chem. Lett.* **2008**, *37*, 954.
6. Hojo, M.; Sakuragi, R.; Okabe, S.; Hosomi, A. *Chem. Commun.* **2001**, 357.
7. (a) Stec, J.; Henderson, A. R.; Whitby, R. J. *Tetrahedron Lett.* **2012**, *53*, 1112; (b) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 3769.
8. (a) Yatsumonji, Y.; Atake, Y.; Tsubouchi, A.; Takeda, T. *Chem. Commun.* **2009**, 3375; (b) Takeda, T.; Ando, M.; Sugita, T.; Tsubouchi, A. *Org. Lett.* **2007**, *9*, 2875; (c) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835; (d) Hanazawa, T.; Okamoto, S.; Sato, F. *Org. Lett.* **2000**, *2*, 2369; (e) Kasatkin, A.; Sato, F. *Angew. Chem., Int. Ed.* **1996**, *35*, 2848; (f) Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225.
9. (a) Kurono, N.; Sugita, K.; Tokuda, M. *Tetrahedron* **2000**, *56*, 847; (b) Nakagawa, T.; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3207; (c) Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768.
10. (a) Ramón, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126; (b) Odom, A. L. *Dalton Trans.* **2005**, 225; (c) Parrish, J. D.; Shelton, D. R.; Little, R. D. *Org. Lett.* **2003**, *5*, 3615; (d) Ding, Y.; Zhao, Z.; Zhou, C. *Tetrahedron* **1997**, *53*, 2899.
11. (a) Chen, L.; Zhao, G.; Ding, Y. *Tetrahedron Lett.* **2003**, *44*, 2611; (b) Yang, F.; Zhao, G.; Ding, Y.; Zhao, Z.; Zheng, Y. *Tetrahedron Lett.* **2002**, *43*, 1289; (c) Yang, F.; Zhao, G.; Ding, Y. *Tetrahedron Lett.* **2001**, *42*, 2839.
12. (a) Justicia, J.; Sancho-Sanz, I.; Álvarez-Manzaneda, E.; Oltra, J. E.; Cuerva Juan, M. *Adv. Synth. Catal.* **2009**, *351*, 2295; (b) Estévez, R. E.; Paradas, M.; Millan, A.; Jimenez, T.; Robles, R.; Cuerva Juan, M.; Oltra, J. E. *J. Org. Chem.* **2008**, *73*, 1616; (c) Rosales, A.; Oller-Lopez, J. L.; Justicia, J.; Gansauer, A.; Oltra, J. E.; Cuerva Juan, M. *Chem. Commun.* **2004**, 2628.
13. Fleury, L. M.; Kosal, A. D.; Masters, J. T.; Ashfeld, B. L. *J. Org. Chem.* **2013**, *78*, 253.
14. (a) Lepore, A. J.; Pinkerton, D. M.; Ashfeld, B. L. *Adv. Synth. Catal.* **2013**, *355*, 1500; (b) Campos, C. A.; Gianino, J. B.; Ashfeld, B. L. *Org. Lett.* **2013**, *15*, 2656; (c) Gianino, J. B.; Ashfeld, B. L. *J. Am. Chem. Soc.* **2012**, *134*, 18217; (d) Campos, C. A.; Gianino, J. B.; Pinkerton, D. M.; Ashfeld, B. L. *Org. Lett.* **2011**, *13*, 5680.
15. Motoyama, Y.; Nishimaya, H. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 59.
16. (a) Kim, C.; Lee, J.; Cho, J.; Oh, Y.; Choi, Y. K.; Choi, E.; Park, J.; Kim, M.-J. *J. Org. Chem.* **2013**, *78*, 2571; (b) Tyrrell, E.; Hunie Tesfa, K.; Mann, A.; Singh, K. *Synthesis* **2007**, 1491; (c) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017.
17. Bejjani, J.; Botuha, C.; Chemla, F.; Ferreira, F.; Magnus, S.; Pérez-Luna, A. *Organometallics* **2012**, *31*, 4876.
18. Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565.