Intermolecular Bromoesterification of Conjugated Enynes: An Efficient Synthesis of Bromoallenes

Journal:	*Organic Chemistry Frontiers*
Manuscript ID:	QO-RES-12-2013-000088.R1
Article Type:	Research Article
Date Submitted by the Author:	12-Feb-2014
Complete List of Authors:	Wang, Hao-Yuan; University of Wisconsin, School of Pharmacy Zhang, Wei; University of Wisconsin, School of Pharmacy Schienebeck, Casi; University of Wisconsin-Madison, School of Pharmacy Bennett, Scott; University of Wisconsin, School of Pharmacy Tang, Weiping; University of Wisconsin, School of Pharmacy

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Intermolecular Bromoesterification of Conjugated Enynes: An Efficient Synthesis of Bromoallenes

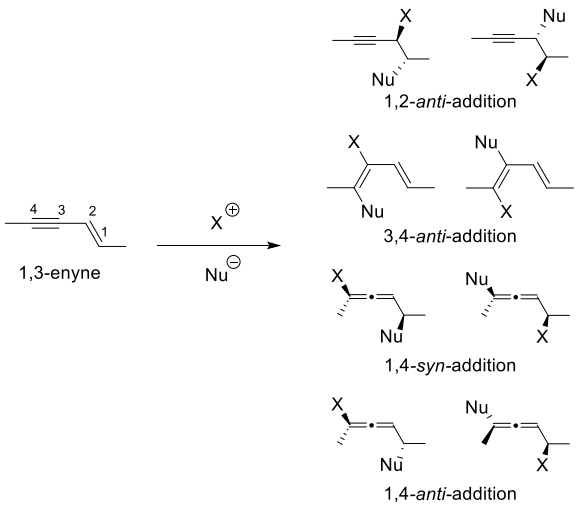
Hao-Yuan Wang,[a] Wei Zhang,[a] Casi M. Schienebeck,[a] Scott R. Bennett,[a] and Weiping Tang*[a,b]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

We have discovered that bromine electrophile and carboxylate nucleophile can be added to conjugated enynes intermolecularly in a 1,4-fashion with high diastereoselectivity. Highly functionalized bromoallenes with an adjacent stereogenic centre were prepared from readily available conjugated 1,3-enynes.

Halogen mediated addition of nucleophiles to alkenes is one of the most fundamentally important reactions.[1, 2] It provides useful building blocks with up to two adjacent new stereogenic centres. Halogen-mediated 1,4-addition to conjugated enynes can produce chiral allenes[3-6] together with a stereogenic centre. This potentially very useful reaction, however, received very little attention partially due to the complex regio- and diastereoselectivity issue as illustrated in Scheme 1.



Scheme 1. Potential Isomeric Products from Halogen-Mediated Addition of Nucleophiles to 1,3-Enynes

The regioselectivity can be overcome partially by tethering the nucleophile with the 1,3-enyne. Indeed, examples of intramolecular halocyclizations in an 1,4-addition fashion have been documented in the literature. In 1982, the first intramolecular bromoetherification of 1,3-enynes was reported in a biomimetic synthesis of racemic panacene (Figure 1).[7, 8] The diastereomeric ratio for this 1,4-addition was 1:1. It was later found that the relative stereochemistry of panacene was assigned wrong.[9] No or low diastereoselectivity were observed for similar intramolecular bromoetherification of 1,3-enynes in the synthesis of laurallene,[10] and kumausallene[11, 12] with a few exceptions.[13, 14] The first stereoselective biomimetic synthesis of bromoallene-containing natural products was accomplished by us in 2011.[15] Nearly perfect diastereoselectivity was observed in the biomimetic intramolecular 1,4-bromoetherification of 1,3-enynes in our enantioselective synthesis of kumausallene.

In addition to panacene, laurallene, and kumausallene, the bromoallene moiety is also present in dozens of other natural products (Figure 1).[16, 17] Only a small portion of them have been synthesized to date.[18-25] Interestingly, all haloallenes found in nature are disubstituted bromoallenes. Haloallene is also an important intermediate for the preparation of more complex allenes and other functional groups.[26-44]

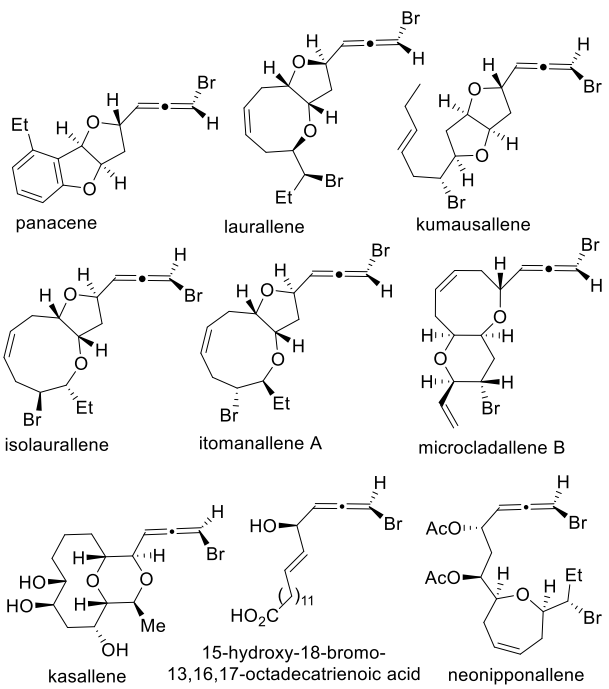
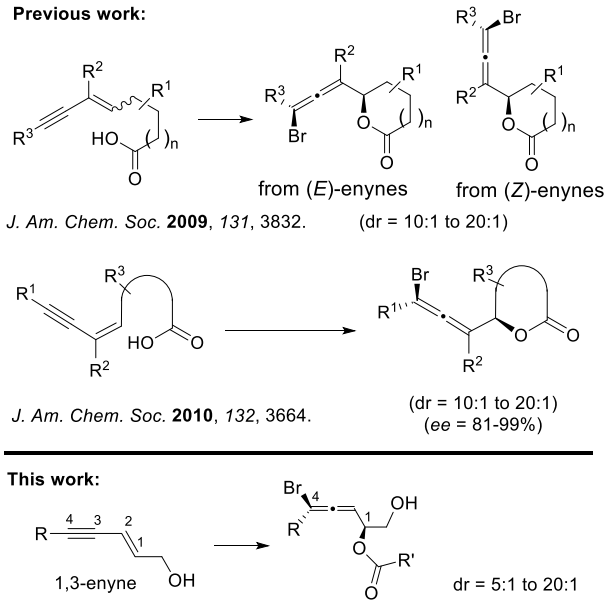


Figure 1. Selected Bromoallene-Containing Natural Products

In 2009, we reported the first 1,4-bromolactonization of

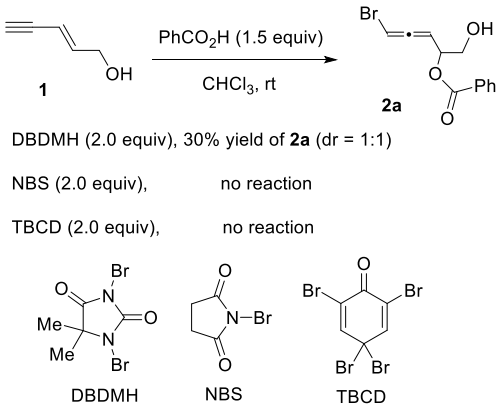
1,3-enynes (Scheme 2).[45] Subsequently, the catalytic asymmetric version of this halocyclization was developed by us,[46] which represents the first catalytic asymmetric halolactonization with more than 90% *ee*.[47] A number of groups[48-65] including us[66] also developed different catalysts for asymmetric halolactonization of substituted alkenes and alkynes. In addition to carboxylate nucleophiles, we also demonstrated that high diastereoselectivity could be achieved for certain nitrogen nucleophiles in several halocyclizations.[67] To the best of our knowledge, the much more challenging halogen-mediated *intermolecular* 1,4-addition to 1,3-enynes has never been reported for any nucleophiles. We herein describe the first example of *intermolecular* 1,4-addition of halogen and carboxylate to 1,3-enynes.



Scheme 2. Intra- and Intermolecular 1,4-Bromoesterification of 1,3-Enynes

Since enyne **1** is commercially available, we began our investigation on the intermolecular bromoesterification with this substrate. We first examined the source of halogen in the absence of any additive (Scheme 3). Around 30% yield of desired 1,4-addition product **2a** was observed with a 1:1 dr when DBDMH was employed, while no reaction occurred using NBS or TBCD.

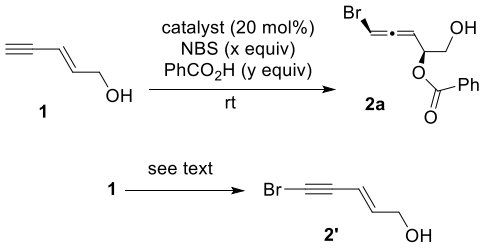
To avoid the background reaction, which provides low diastereoselectivity, we then examined different catalysts that can activate NBS (entries 1-5, Table 1). Similar to the intramolecular reaction,[45] DABCO afforded the highest diastereoselectivity (entry 1). The major diastereomer was assigned as syn-addition product shown in Table 1 based on our previous studies on halocyclization of enynes.[17, 18, 39] We next investigated the effect of the amount of NBS to the dr and yield in the presence of 1.1 equivalent of benzoic acid (entries 6-8). Both dr and yield were increased with less NBS reagent. Other solvents (entries 9 and 10) gave poor results. The best yield was obtained when the amount of benzoic acid was increased from 1.1 to 1.3 equivalents (entry 11). Although the yield of **2a** could be improved further with more benzoic acids (entry 12), the dr dropped from 10:1 to 7:1.



Scheme 3. 1,4-Bromoesterification of 1,3-Enyne **1** with Different Halogenation Reagents

We also replaced NBS with TBCD under conditions in entry 6 of Table 1. Interestingly, the only product we observed was bromoalkyne **2'**, where the hydrogen atom on the terminal alkyne was replaced by a bromine atom.

Table 1. Screening of Conditions for 1,4-addition of Benzoate and Bromine to 1,3-Enyne **1**

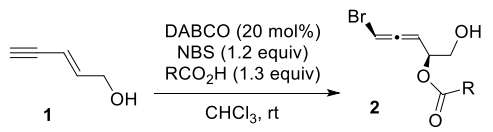


entry	catalyst	x	y	solvent	dr	Yield[a]
1	DABCO	2.0	1.5	$CHCl_3$	5:1	41%
2	DBU	2.0	1.5	$CHCl_3$	1:1	<10%
3	DMAP	2.0	1.5	$CHCl_3$	1:1	<10%
4	DMF	2.0	1.5	$CHCl_3$	3:1	31%
5	PPh_3	2.0	1.5	$CHCl_3$	no reaction	
6	DABCO	2.0	1.1	$CHCl_3$	3:1	46%
7	DABCO	1.5	1.1	$CHCl_3$	5:1	63%
8	DABCO	1.2	1.1	$CHCl_3$	10:1	65%
9	DABCO	1.2	1.1	DCE	3:1	73%
10	DABCO	1.2	1.1	toluene	no reaction	
11	DABCO	1.2	1.3	$CHCl_3$	10:1	75%
12	DABCO	1.2	1.5	$CHCl_3$	7:1	83%

[a.] Yield was based on NMR using CH_2Br_2 as the internal standard.

With the optimized condition (entry 11, Table 1) in hand, we then studied the scope of the carboxylic acids (Table 2). Similar results were obtained by using *ortho*- or *para*-methyl substituted benzoic acids (entries 2 and 3). A slower reaction was observed for benzoic acid with a strong electron-donating group (entry 4), while benzoic acid with a strong electron-withdrawing group yielded a complex mixture (entry 5). Halogen substituted benzoic acids gave 44% to 70% yields of the desired products (entries 6-8). Lower yields for entries 7 and 8 are likely due to the poor solubility of the corresponding benzoic acids. Aliphatic carboxylic acids generally worked well with slightly lower dr (entries 9-11).

Table 2. Scope of Carboxylic Acids

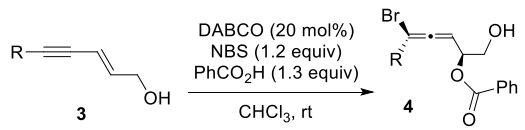


entry	carboxylic acid (R)	product	dr	Yield[a]
1	R = C_6H_5	**2a**	10:1	73%
2	R = *o*-$CH_3C_6H_4$	**2b**	10:1	65%
3	R = *p*-$CH_3C_6H_4$	**2c**	10:1	65%
4	R = *p*-$CH_3OC_6H_4$	**2d**	10:1	45%
5	R = *p*-$NO_2C_6H_4$	complex mixture		
6	R = *p*-FC_6H_4	**2e**	10:1	70%
7	R = *p*-ClC_6H_4	**2f**	10:1	45% (60%)[b]
8	R = *p*-BrC_6H_4	**2g**	10:1	44% (57%)[b]
9	R = CH_3	**2h**	8:1	67%
10	R = $C_6H_5CH_2$	**2i**	5:1	77%
11	R = CH_3CH_2	**2j**	5:1	61%

[a] Isolated yield. [b] Based on recovered starting material.

The scope of enynes was also examined (Table 3). Enynes with sterically bulky groups provided higher diastereoselectivity compared with **2** (entries 1 and 2). The dr and yield for enyne **3c** with a long-chain aliphatic substituent (entry 3) were similar to the parent substrate **1**. No reaction occurred for enynes with an aryl or cyclopropyl substituent (entries 4 and 5).

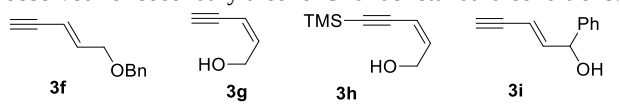
Table 3. Scope of Enynes



entry	enyne (R)	product	dr	Yield[a]
1	**3a**, R = *t*Bu	**4a**	20:1	71%
2	**3b**, R = TMS	**4b**	14:1	71%
3	**3c**, R = $CH_3(CH_2)_5$	**4c**	10:1	65%
4	**3d**, R = C_6H_5		no reaction	
5	**3e**, R = cyclopropyl		no reaction	

[a] Isolated yield.

We also found that the free hydroxyl group in **1** was required since no reaction occurred for substrate **3f**, where the OH group was masked as benzyl ether (Scheme 4). Surprisingly, enynes **3g** and **3h** with a cis-alkene also did not afford any desired products. Only trace amount of product was observed for secondary alcohol **3i** under standard conditions.



Scheme 4. Failed Substrates

Similar to previously reported intramolecular 1,4-addition of halogen and nucleophile to 1,3-enynes,[17, 18, 39] the overall syn-addition is likely due to the interaction between the negatively charged carboxylate and partially positively charged electrophile. The free OH group may facilitate the addition by forming a hydrogen-bond with the carboxylate.

In summary, we have developed the first intermolecular 1,4-bromoesterification of conjugated 1,3-enynes. Functionalized bromoallenes were prepared efficiently from relative simple starting materials diastereoselectively. Broad range of carboxylic acids and enynes with either a terminal or internal alkyne can participate in the 1,4-addition reaction.

Experimental Section

General procedure for the intermolecular 1,4-bromoesterification of conjugated enynes:

To a 6 mL vial was added enyne **1** (0.1 mmol, 8.2 mg), DABCO (0.02 mmol, 2.2 mg), and benzoic acid (0.13 mmol, 15.9 mg). To the above mixture was added 1 mL of $CHCl_3$. Subsequently, NBS (0.12 mmol, 21.4 mg) was added to the above solution. The reaction was stirred at room temperature until enyne **1** was consumed as indicated by TLC. The reaction was filtered through a short silica gel column. ^1H NMR analysis of the crude mixture was performed to obtain the dr. The mixture was then purified by flash column chromatograph using hexane and ethyl acetate (4:1) as the eluent. Product **2a** was obtained as a colorless oil in 73% yield (21.0 mg, dr = 10:1). The reaction was scaled up to 1 mmol for the preparation of **2a** (dr = 10:1, 68% yield).

Acknowledgements

We thank the University of Wisconsin for financial support and a Young Investigator Award from Amgen (to W. T.).

Notes and references

[a] *School of Pharmacy, University of Wisconsin, Madison, WI, 53705 USA.*
[b] *Department of Chemistry, University of Wisconsin, Madison, WI,53706 USA.*
E-mail: wtang@pharmacy.wisc.edu

† Electronic Supplementary Information (ESI) available: [^1H NMR, ^{13}C NMR, HRMS, and IR data and copies of NMR specta for all starting materials and products.]. See DOI: 10.1039/b000000x/

1. K. E. Harding and T. H. Tiner, in *Comprehensive Organic Synthesis*, eds. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 4, p. 363.
2. J. Rodriguez and J. P. Dulcere, *Synthesis*, 1993, 1177.
3. N. Krause and A. S. K. Hashmi, *Modern Allene Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2004.
4. S. Ma, *Chem. Rev.*, 2005, **105**, 2829.
5. K. M. Brummond and J. E. DeForrest, *Synthesis*, 2007, 795.
6. S. Yu and S. Ma, *Chem. Commun.*, 2011, **47**, 5384.
7. K. S. Feldman, C. C. Mechem and L. Nader, *J. Am. Chem. Soc.*, 1982, **104**, 4011.
8. K. S. Feldman, *Tetrahedron Lett.*, 1982, **23**, 3031.
9. J. Boukouvalas, M. Pouliot, J. Robichaud, S. MacNeil and V. Snieckus, *Org. Lett.*, 2006, **8**, 3597.
10. J. Ishihara, Y. Shimada, N. Kanoh, Y. Takasugi, A. Fukuzawa and A. Murai, *Tetrahedron*, 1997, **53**, 8371.
11. M. T. Crimmins and E. A. Tabet, *J. Am. Chem. Soc.*, 2000, **122**, 5473.
12. P. A. Evans, V. S. Murthy, J. D. Roseman and A. L. Rheingold, *Angew. Chem. Int. Ed.*, 1999, **38**, 3175.
13. D. C. Braddock, R. Bhuva, Y. Perez-Fuertes, R. Pouwer, C. A. Roberts, A. Ruggiero, E. S. E. Stokes and A. J. P. White, *Chem. Commun.*, 2008, 1419.
14. C. Sabot, D. Berard and S. Canesi, *Org. Lett.*, 2008, **10**, 4629.
15. J. B. Werness and W. Tang, *Org. Lett.*, 2011, **13**, 3664.
16. A. Hoffmann-Röder and N. Krause, *Angew. Chem. Int. Ed.*, 2004, **43**, 1196.

17. V. M. Dembitsky and T. Maoka, *Progress Lipid Res.*, 2007, **46**, 328.
18. T. A. Grese, K. D. Hutchinson and L. E. Overman, *J. Org. Chem.*, 1993, **58**, 2468.
19. J. Wang and B. L. Pagenkopf, *Org. Lett.*, 2007, **9**, 3703.
20. T. Saitoh, T. Suzuki, M. Sugimoto, H. Hagiwara and T. Hoshi, *Tetrahedron Lett.*, 2003, **44**, 3175.
21. M. T. Crimmins and K. A. Emmitte, *J. Am. Chem. Soc.*, 2001, **123**, 1533.
22. M. T. Crimmins, K. A. Emmitte and A. L. Choy, *Tetrahedron*, 2002, **58**, 1817.
23. J. Park, B. Kim, H. Kim, S. Kim and D. Kim, *Angew. Chem. Int. Ed.*, 2007, **46**, 4726.
24. W. Jeong, M. J. Kim, H. Kim, S. Kim, D. Kim and K. J. Shin, *Angew. Chem. Int. Ed.*, 2010, **49**, 752.
25. M. J. Kim, T.-i. Sohn, D. Kim and R. S. Paton, *J. Am. Chem. Soc.*, 2012, **134**, 20178.
26. J. A. Marshall and N. D. Adams, *J. Org. Chem.*, 1997, **62**, 8976.
27. H. Ohno, H. Hamaguchi and T. Tanaka, *Org. Lett.*, 2001, **3**, 2269.
28. H. Ohno, K. Ando, H. Hamaguchi, Y. Takeoka and T. Tanaka, *J. Am. Chem. Soc.*, 2002, **124**, 15255.
29. H. Ohno, H. Hamaguchi, M. Ohata, S. Kosaka and T. Tanaka, *J. Am. Chem. Soc.*, 2004, **126**, 8744.
30. H. Hamaguchi, S. Kosaka, H. Ohno and T. Tanaka, *Angew. Chem. Int. Ed.*, 2005, **44**, 1513.
31. B. Xu and G. B. Hammond, *Angew. Chem. Int. Ed.*, 2005, **44**, 7404.
32. B. M. Trost and D. T. Stiles, *Org. Lett.*, 2005, **7**, 2117.
33. S. Ma and H. Xie, *Tetrahedron*, 2005, **61**, 251.
34. L. C. Shen, R. P. Hsung, Y. S. Zhang, J. E. Antoline and X. J. Zhang, *Org. Lett.*, 2005, **7**, 3081.
35. C. J. Tang and Y. K. Wu, *Tetrahedron*, 2007, **63**, 4887.
36. B. Vaz, M. Dominguez, R. Alvarez and A. R. de Lera, *Chem. Eur. J.*, 2007, **13**, 1273.
37. H. Hamaguchi, S. Kosaka, H. Ohno, N. Fujii and T. Tanaka, *Chem. Eur. J.*, 2007, **13**, 1692.
38. Y. Z. Xia, A. S. Dudnik, V. Gevorgyan and Y. H. Li, *J. Am. Chem. Soc.*, 2008, **130**, 6940.
39. Y. Tang, L. Shen, B. J. Dellaria and R. P. Hsung, *Tetrahedron Lett.*, 2008, **49**, 6404.
40. A. K. A. Persson and J.-E. Bäckvall, *Angew. Chem. Int. Ed.*, 2010, **49**, 4624.
41. T. Jiang, A. K. A. Persson and J.-E. Bäckvall, *Org. Lett.*, 2011, **13**, 5838.
42. A. K. A. Persson, T. Jiang, M. T. Johnson and J.-E. Bäckvall, *Angew. Chem. Int. Ed.*, 2011, **50**, 6155.
43. Y. Deng, T. Bartholomeyzik, A. K. A. Persson, J. Sun and J.-E. Bäckvall, *Angew. Chem. Int. Ed.*, 2012, **51**, 2703.
44. H. Chiba, Y. Sakai, A. Ohara, S. Oishi, N. Fujii and H. Ohno, *Chem. Eur. J.*, 2013, **19**, 8875.
45. W. Zhang, H. D. Xu, H. Xu and W. Tang, *J. Am. Chem. Soc.*, 2009, **131**, 3832.
46. W. Zhang, S. Zheng, N. Liu, J. B. Werness, I. A. Guzei and W. Tang, *J. Am. Chem. Soc.*, 2010, **132**, 3664.
47. G. Chen and S. Ma, *Angew. Chem. Int. Ed.*, 2010, **49**, 8306.
48. D. C. Whitehead, R. Yousefi, A. Jaganathan and B. Borhan, *J. Am. Chem. Soc.*, 2010, **132**, 3298.
49. R. Yousefi, D. C. Whitehead, J. M. Mueller, R. J. Staples and B. Borhan, *Org. Lett.*, 2011, **13**, 608.
50. R. Yousefi, K. D. Ashtekar, D. C. Whitehead, J. E. Jackson and B. Borhan, *J. Am. Chem. Soc.*, 2013, **135**, 14524.
51. L. Zhou, C. K. Tan, X. Jiang, F. Chen and Y.-Y. Yeung, *J. Am. Chem. Soc.*, 2010, **132**, 15474.
52. C. K. Tan, L. Zhou and Y.-Y. Yeung, *Org. Lett.*, 2011, **13**, 2738.
53. J. Chen, L. Zhou, C. K. Tan and Y.-Y. Yeung, *J. Org. Chem.*, 2012, **77**, 999.
54. C. K. Tan, C. Le and Y.-Y. Yeung, *Chem. Commun.*, 2012, **48**, 5793.
55. X. Jiang, C. K. Tan, L. Zhou and Y.-Y. Yeung, *Angew. Chem. Int. Ed.*, 2012, **51**, 7771.
56. G. E. Veitch and E. N. Jacobsen, *Angew. Chem. Int. Ed.*, 2010, **49**, 7332.
57. K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura and H. Fujioka, *Angew. Chem. Int. Ed.*, 2010, **49**, 9174.
58. K. Murai, A. Nakamura, T. Matsushita, M. Shimura and H. Fujioka, *Chem. Eur. J.*, 2012, **18**, 8448.
59. K. Murai, T. Matsushita, A. Nakamura, N. Hyogo, J. Nakajima and H. Fujioka, *Org. Lett.*, 2013, **15**, 2526.
60. M. C. Dobish and J. N. Johnston, *J. Am. Chem. Soc.*, 2012, **134**, 6068.
61. J. E. Tungen, J. M. J. Nolsoe and T. V. Hansen, *Org. Lett.*, 2012, **14**, 5884.
62. D. H. Paull, C. Fang, J. R. Donald, A. D. Pansick and S. F. Martin, *J. Am. Chem. Soc.*, 2012, **134**, 11128.
63. C. Fang, D. H. Paull, J. C. Hethcox, C. R. Shugrue and S. F. Martin, *Org. Lett.*, 2012, **14**, 6290.
64. K. Ikeuchi, S. Ido, S. Yoshimura, T. Asakawa, M. Inai, Y. Hamashima and T. Kan, *Org. Lett.*, 2012, **14**, 6016.
65. M. Wilking, C. Mueck-Lichtenfeld, C. G. Daniliuc and U. Hennecke, *J. Am. Chem. Soc.*, 2013, **135**, 8133.
66. W. Zhang, N. Liu, C. M. Schienebeck, K. Decloux, S. Zheng, J. B. Werness and W. Tang, *Chem. Eur. J.*, 2012, **18**, 7296.
67. N. Liu, J. B. Werness, I. A. Guzei and W. Tang, *Tetrahedron* 2011, **67**, 4385.