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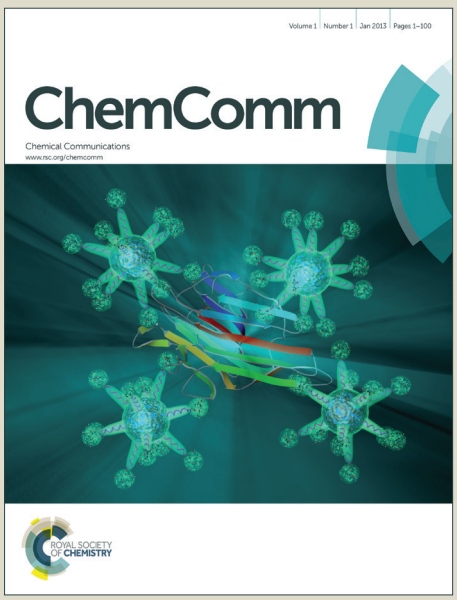

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Au (I)-Catalyzed Synthesis of 8-Oxabicyclo[3.2.1]oct-2-enes and 9-Oxabicyclo[3.3.1]nona-2,6-dienes from Enynol via Oxonium/Prins-type Cyclization

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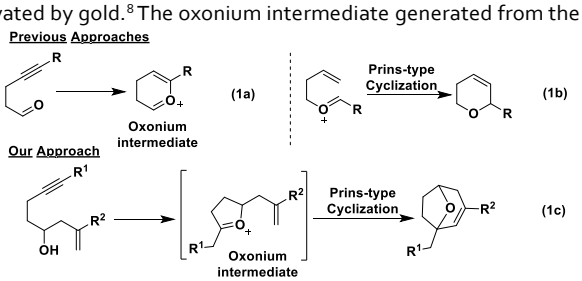
A sustainable and simple Au^{I} catalytic system to synthesis 8-oxabicyclo[3.2.1]oct-2-ene and 9-oxabicyclo[3.3.1]nona-2,6-dienes from enynol via oxonium/Prins-type cyclization is described. The key advantages of this reaction are selectivity, good functional group tolerance and a new approach for synthesis of oxabicyclic and oxatricyclic systems.

Gold catalyzed reactions are powerful tools that are used to promote a broad range of organic transformations to form C-C and C-X bonds by activating the C–C multiple bonds towards intra- or inter-nucleophilic attack.[1] Most reports depend on the π- acidity of either gold(I) or gold(III) complexes to trigger multiple bonds toward nucleophilic attack, followed by protodeauration.[2-7] Therefore, gold catalyzed reactions afford direct and atom-economical synthetic approaches for constructing complex heterocycles from simple starting materials.

Recently, many research groups have focused on highly reactive oxonium intermediates produced *in situ* by the intramolecular cyclization of enynone or enynal analogs, which are electrophilically activated by gold.[8] The oxonium intermediate generated from the enynol system has been far less studied in the presence of gold, so there is a need to explore this area to produce complex molecules.[9] In terms of generating the oxonium intermediate, *endo-dig* cyclizations have been well studied (Scheme 1, 1a)[8] but *exo*-dig cyclizations have been less often documented.[8b]



Scheme 1. Approach to synthesis oxacyclic compounds.

Generally, the acyclic oxonium intermediates react with nucleophiles to generate heterocyclic systems via a Prins-type cyclization (Scheme 1, 1b).[10] Only a few reports have described the attack of nucleophilic olefin into a cyclic oxonium cation to give polycyclic compounds.[11] In this context, we were interested in examining a new cascade annulation by using gold from an enynol system to generate a cyclic oxonium cation followed by a Prins-type cyclization to give oxacyclic analogs (Scheme 1, 1c).

Oxacyclic cores most commonly occurring in natural products and they also have significant importance in medicinal chemistry.[12] Of note, the oxatricyclic moieties have shown potency towards HIV-1 inhibition and central nervous system diseases (Figure 1).[13] To date, only one report by the Liu group has addressed synthesising 9-oxabicyclo [3.3.1]nona-2,6-dienes **3** from 2-alkynyl-1-carbonylbenzenes **1** and allylsilanes **2** in the presence of $PtCl_2$/CO (Scheme 2, 2a).[9a] Thus, the opportunity for developing efficient methods for the synthesis of these biologically important cores is of utmost urgency. Herein, we report a new system to synthesize compound **6** or **7** from ortho-alkynylaryl alcohol derivatives **4**/**5** in the

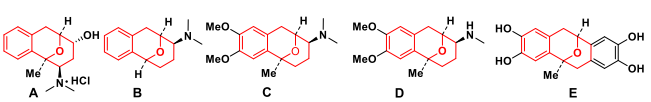
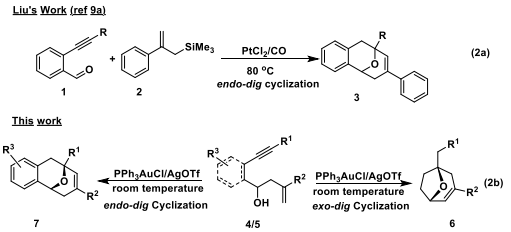


Figure 1. Biologically potent molecules with oxatricyclic frameworks.

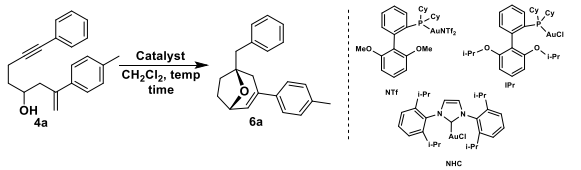
presence of Au/Ag (Scheme 2, 2b) under mild conditions. This reaction follows via *exo*- or *endo-dig* cyclization, depending on the substrate structure (**4** or **5**). Generally, the alkyne attached with a fully saturated linker preferably proceeds via 5-*exo-dig* cyclization (compound **4**).[14] Whereas, in the alkyne connected with conjugated or strained fused ring systems (compound **5**), the 6-*endo-dig* cyclization was favoured and the *5-exo-dig* was disfavoured due to ring strain.[14] When the R^1 is H or TMS (compound **4**/**5**), the formation of σ-vinylexo anions are favoured mostly in *exo-dig* cyclyization rather than in *endo-dig* cyclization.[14]



Scheme 2. Synthesis of oxacyclic compounds.

Our exploration was initiated with the compound **4a**. The reaction was screened with gold catalysts, PPh_3AuCl and $AuCl_3$ in dichloromethane at reflux for 24h. The reaction was failed to give **6a** (Table 1, entry 1-2). The next trial was performed with $PPh_3AuCl/AgSbF_6$ in dichloromethane. To our delight, the desired compound **6a** was obtained with 42% yield (entry 3). To improve the yield, other silver salts, such as AgOTf and $AgNTf_2$, were screened. Of these, AgOTf showed a better result by producing compound **6a** with 86% yield (entry 4); and, with $AgNTf_2$, a moderate yield (64%) was observed (entry 5). To check the efficiency of the reaction with other gold catalysts, the commercially available 2-dicyclohexyl(2′,6′-dimethoxybiphenyl)phosphine gold(I) bis(trifluoromethylsulfonyl)imide was used; this resulted in a 66% yield (entry 6). The reactions with chloro[2-dicyclohexyl(2′,6′;-diisopropoxybiphenyl)phosphine] gold(I) (entry 7) and chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) (entry 8) were also tested and both afforded the desired compound with yields of 79% and 76%, respectively. In the absence of the gold catalyst, the reaction did not progress (entry 9); thus, a combination of gold and silver is necessary. The $PPh_3AuCl/AgOTf$ combination was shown to be more efficient than the other gold catalysts and further screening was continued using this combination. Dichloromethane provided a better yield for this conversion, compared with the 1,2-dichloroethane (entry 10). When the temperature was elevated to 50 °C, the reaction yield did not change (entry 11). When the time was reduced to 12h, the reaction yield was not affected (entry 12). With 10 mol% of catalyst (entry 13), the reaction yield did not improve, and by reducing the catalyst to 2 mol % the reaction yield decreased (entry 14).

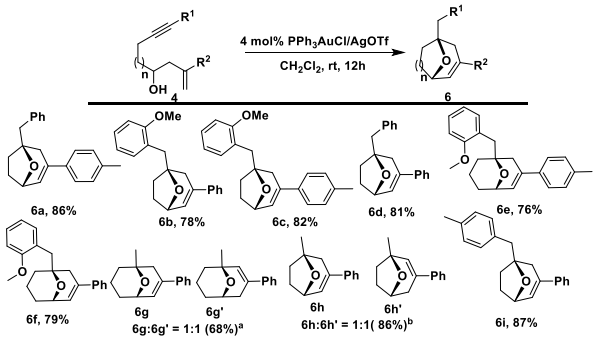
Table 1. Screening of catalysts and solvents for the cascade annulation.[a]



Entry	Catalyst	Temp (°C)	Time	Yield [%]
1	PPh_3AuCl	reflux	24	0
2	$AuCl_3$	reflux	24	0
3	$PPh_3AuCl/AgSbF_6$	28	24	42
4	$PPh_3AuCl/AgOTf$	28	24	86
5	$PPh_3AuCl/AgNTf_2$	28	24	64
6	NTf	28	24	66
7	IPr/AgOTf	28	24	79
8	NHC/AgOTf	28	24	76
9	AgOTf	28	24	0
10[b]	$PPh_3AuCl/AgOTf$	28	24	73
11	$PPh_3AuCl/AgOTf$	50	24	85
12	$PPh_3AuCl/AgOTf$	28	12	86
13[c]	$PPh_3AuCl/AgOTf$	28	24	86
14[d]	$PPh_3AuCl/AgOTf$	28	24	72

[a] Reaction conditions: **4** (0.1 mmol) and catalyst (4 mol %), and in solvent (3 mL). Isolated yield. [b] 1,2-dichloroethane. [c] 10 mol % of catalyst. [d] 2 mol % of catalyst.

Table 2. Scope of the reaction to synthesis oxabicyclic compounds.

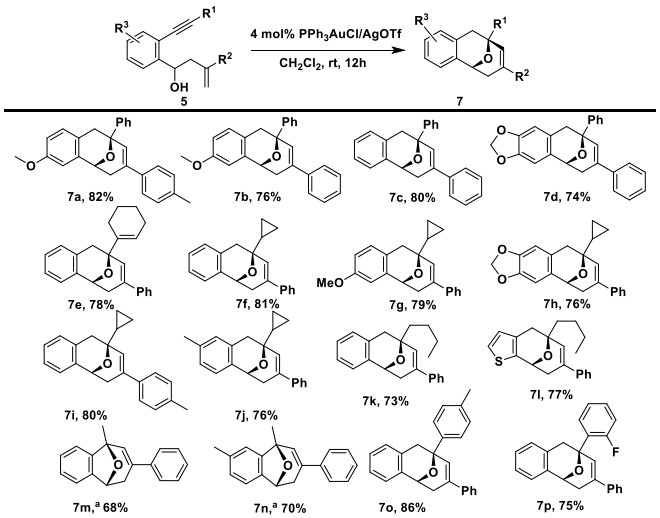


[a] R^1 =H. [b] R^1 = TMS.

Under the optimized conditions at hand (Table 1, entry 12), the scope of the oxabicyclic compounds were studied (Table 2). The reaction smoothly progressed with the various substituents on the phenyl rings (Table 2, **6a**-**6f** and **6i**) via *exo-dig* mode cyclization. The reaction was highly regioselective by producing a single isomer in moderate to good yields. The ring size was increased from five to six members and the reaction successfully afforded **6e** and **6f**. When R^1 was hydrogen or the TMS group, the regioisomers were observed in a 1:1 ratio with yield 68% as **6g** and **6g'**; similarly **6h** and **6h'** were also observed in a 1:1 ratio with good yield (86%). The structure of **6d** was confirmed by X-ray analysis.[15]

Next, the scope was extended to prepare oxatricyclic compounds under optimized conditions, as shown in Table 3. In contrast to the oxabicyclic compounds (Table 2), the oxatricyclic compounds (Table 3) proceeded via an *endo-dig* cyclization. When the R^3 was substituted for various groups, the reaction progressed well to give moderate to good yields (**7a**-**7d**). When R^1 was replaced with cyclohexyl, cyclopropyl and n-butyl, the substitutions were also tolerated well with good yields (**7e**-**7k**). The heterocyclic system as thiophene (**7l**) underwent the reaction smoothly to give a 77% yield. Surprisingly, when R^1 is H or TMS, the reaction proceeds via *exo-dig* cyclization (**7m** and **7n**). Electron donating substituent on the phenyl ring of R^1 tolerated the reaction well with 86% yield (**7o**) and the electron withdrawing group also progressed with a good yield of 75% (**7p**). Attempts to replace the hydroxyl group with amines and thiols were failed. Compounds **7d, 7i** and **7m** were confirmed by X-ray analysis.[15]

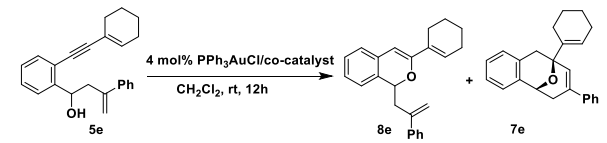
Table 3. Scope of the reaction to synthesis oxatricyclic compounds.



[a] Reaction followed *exo-dig* cyclization with R^1 = H or TMS.

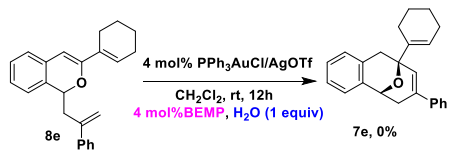
To understand the reaction mechanism, a series of control experiments were performed (Table 4). The intermediate **8e** was confirmed by proton NMR after 6h of reaction (entry 1). Further mechanistic insights were performed, to identify whether the source of the proton was liberated from residual TfOH or moisture. The catalytic amount of tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), a non-poisoning base, was used to understand the reaction. With 4 mol% BEMP, the reaction did not progress and the starting material was recovered (entry 2). By reducing the catalytic amount of BEMP to 1 mol%, the desired compound **7e** was afforded with a 48% yield (entry 3). To confirm the existence of TfOH, the reaction was performed with TfOH

Table 4. Reaction mechanistic Studies.



S.No	Additive	Co-catalyst	**8e** (%)	**7e** (%)
1[a]	--	AgOTf	48	35
2	BEMP (4 mol%)	AgOTf	0	0
3	BEMP (1 mol%)	AgOTf	--	48
4[b]	TfOH (4 mol%)	--	0	0
5	H_2O (1 equiv)	AgOTf	--	76
6	H_2O (1 equiv) + BEMP (4 mol%)	AgOTf	0	0
7[c]	--	AgOTf	20	24

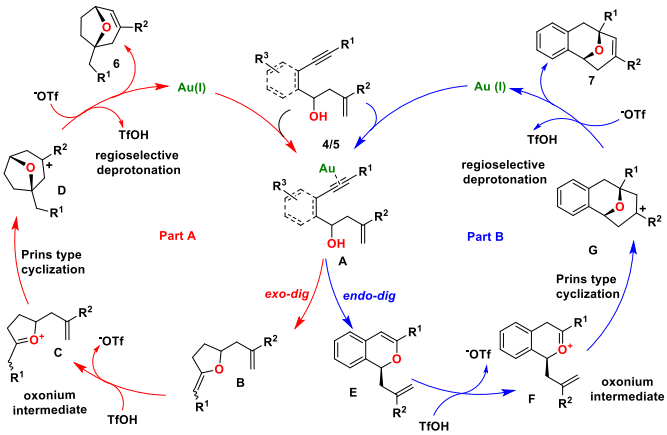
[a] 6h. [b] Complex mixture. [c] In presence of 4Å molecular sieves & dry CH_2Cl_2.



Scheme 4. Control Experiment.

instead of AgOTf and the reaction was decomposed (entry 4), and the probable reason could be the intermediates are not stable under acidic conditions. Next, to confirm the role of water as a proton source, the reaction was performed by adding water (1 equiv) to the reaction; this resulted in a good yield of 76% (entry 5). Another trial was conducted using water (1 equiv) and 4 mol% of BEMP, but it failed to give the desired compound **7e** (entry 6). The reaction yield was reduced by using 4Å molecular sieves in dry CH_2Cl_2 (entry 7). We believe that the water present in the reaction medium may facilitate the TfOH formation, thus the low yield was observed under dry conditions. The intermediate **8e** under optimized conditions with BEMP (4 mol%), the reaction was not progressed (Scheme 4). The control experiments (Table 4, entries 2 & 6, Scheme 4) carried out with BEMP were inhibited, due to the neutralization of residual TfOH. From the above results, we presume that the residual TfOH generated from the catalytic system will be the proton source for the formation of oxonium ion.

From the experimental findings and previous reports,[9a] a plausible mechanism was proposed in Scheme 5. Initially, the intermediate **A** undergoes an *exo-dig* cyclization (Part A) with the aid of the gold catalyst to form intermediate **B**. Then, the intermediate **B** undergoes protonation with the aid of residual TfOH generated from the catalyst to give the oxonium intermediate **C**. The cyclic oxonium intermediate **C** reacts with the nucleophilic alkene via a Prins-type cyclization to give the oxabicyclic tertiary cation **D**. The compound **D** undergoes a regioselective deprotonation to form the desired compound **6** and TfOH was regenerated for next cycle. For the oxatricyclic compounds **7**, the same mechanism was followed via *endo-dig* cyclization.



Scheme 5. A plausible mechanism for *exo-dig* and *endo-dig* cyclization.

In summary, we presented a new approach to construct oxabicyclic and oxatricyclic compounds via a gold (I) catalytic system. The reaction follows a rare kind of pathway, as an oxonium intermediate, which undergoes a nucleophilic alkene attack via a Prins-type cyclization. Further biological studies are in progress.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedures, product characterization, X-rays and copies of NMR spectra. See DOI: 10.1039/c000000x/

1 (a) D. J. Gorin and F. D. Toste, *Nature* 2007, **446**, 395; (b) A. S. K. Hashmi, *Chem. Rev*., 2007, **107**, 3180; (c) Z. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, **108**, 3239; (d) A. Arcadi, *Chem. Rev*., 2008, **108**, 3266; (e) E. J.-Nunez and A. M. Echavarren, *Chem. Rev*., 2008, **108**, 3326; (f) S. M. A. Sohel and R.-S. Liu, *Chem. Soc. Rev*., 2009, **38**, 2269; (g) A. Corma, A. Leyva-Perez, and M. J. Sabater, *Chem. Rev*., 2011, **111**, 1657; (h) N. Krause and C. Winter, *Chem. Rev*., 2011, **111**, 1994; (i) T. C. Boorman and I. Larrosa, *Chem. Soc. Rev*., 2011, **40**, 1910; (j) H. Schmidbaur, H. G. Raubenheimer and L. Dobrzansk, *Chem. Soc. Rev*., 2014, **43**, 345; (k) D. Qiana and J. Zhang, *Chem. Soc. Rev*., 2015, **44**, 677; (l) J. Xie, C. Pan, A. Abdukader and C. Zhu, *Chem. Soc. Rev*., 2014, **43**, 5245.

2 (a) W. Wang, G. B. Hammond and B. Xu, *J. Am. Chem. Soc*., 2012, **134**, 5697; (b) Y. Tang, J. Li, Y. Zhu, Y. Li and B. Yu, *J. Am. Chem. Soc*., 2013, **135**, 18396; (c) X.-Z. Shu, M. Zhang, Y. He, H. Frei and F. D. Toste, *J. Am. Chem. Soc*., 2014, **136**, 5844; (d) C. R. S.-Alvarado and A. M. Echavarren, *J. Am. Chem. Soc*., 2010, **132**, 11881.

3 (a) A. M. Jadhav, S. Bhunia, H.-Y. Liao and R.-S. Liu, *J. Am. Chem. Soc*., 2011, **133**, 1769; (b) C.-H. Chen, Y.-C. Tsai and R.-S. Liu, *Angew. Chem. Int. Ed*., 2013, **52**, 4599; (c) S. K. Pawar, C.-D. Wang, S. Bhunia, A. M. Jadhav and R.-S. Liu, *Angew. Chem. Int. Ed*., 2013, **52**, 7559; (d) S. N. Karad and R.-S. Liu, *Angew. Chem. Int. Ed*., 2014, **53**, 9072; (e) V. V. Pagar and R.-S. Liu, *Angew. Chem. Int. Ed*., 2015, 54, 4923.

4 (a) S. Mader, L. Molinari, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Chem. -Eur. J*., 2015, **21**, 3910; (b) P. Nösel, V. Müller, S. Mader, S. Moghimi, M. Rudolph, I. Braun, F. Rominger and A. S. K. Hashmi, *Adv. Synth. Catal*., 2015, **357**, 500; (c) Y. Tokimizu, M. Wieteck, M. Rudolph, S. Oishi, N. Fujii, A. S. K. Hashmi and H. Ohno, *Org. Lett*., 2015, **17**, 604; (d) M. C. B. Jaimes, A. Ahrens, M. Rudolph and A. S. K. Hashmi, *Chem. -Eur. J*., 2015, **21**, 427.

5 (a) L. Zhang, *Acc. Chem. Res*., 2014, **47**, 877; (b) J. Li, K. Ji, R. Zheng, J. Nelson and L. Zhang, *Chem. Commun*., 2014, **50**, 4130.

6 (a) Y. Wang, M. E. Muratore, Z. Rong and A. M. Echavarren, *Angew. Chem. Int. Ed*., 2014, **53**, 14022; (b) D. Leboeuf, M. Gaydou, Y. Wang and A. M. Echavarren, *Org. Chem. Front*., 2014, **1**, 759; (c) A. Homs, C. Obradors, D. Leboeuf and A. M. Echavarren, *Adv. Synth. Catal*., 2014, **356**, 221; (d) C. Obradors and A. M. Echavarren, *Acc. Chem. Res*., 2014, **47**, 902; (e) M. Livendahl, C. Goehry, F. Maseras and A. M. Echavarren, *Chem. Commun*., 2014, **50**, 1533; (f) C. Obradors and A. M. Echavarren, *Chem. Commun*., 2014, **50**, 16; (g) Y. Wang, P. R. McGonigal, B. Herlé, M. Besora, and A. M. Echavarren, *J. Am. Chem. Soc*. 2014, **136**, 801.

7 (a) N. T. Patil, A. K. Mutyala, A. Konala and R. B. Tella, *Chem. Commun*., 2012, **48**, 3094; (b) N. T. Patil, V. S. Raut and R. B. Tella, *Chem. Commun*., 2013, **49**, 570; (c) V. S. Shinde, M. V. Mane, K. Vanka, A. Mallick and N. T. Patil, *Chem. -Eur. J*., 2015, **21**, 975; (d) A. H. Bansode, A. C. Shaikh, R. D. Kavthe, S. Thorat R. G. Gonnade and N. T. Patil, *Chem. -Eur. J*., 2015, **21**, 2319; (e) P. N. Bagle, V. S. Shinde and N. T. Patil, *Chem. -Eur. J*., 2015, **21**, 3580.

8 (a) N. Asao, T. Kasahara and Y. Yamamoto, *Angew. Chem. Int. Ed*., 2003, **42**, 3504; (b) T.-M. Teng, A. Das, D. B. Huple and R.-S. Liu, *J. Am. Chem. Soc*., 2010, **132**, 12565; (c) S.-Y. Yu, H. Zhang, Y. Gao, L. Mo, S. Wang, and Z.-J. Yao, *J. Am. Chem. Soc*., 2013, **135**, 11402; (d) K. Saito, Y. Kajiwara and T. Akiyama, *Angew. Chem. Int. Ed*., 2013, **52**, 13284; (e) J.-R. Chen, X.-Q. Hu and W.-J. Xiao, *Angew. Chem. Int. Ed*., 2014, **53**, 4038; (f) S. Zhu, X. Huang, T.-Q. Zhao, T. Maa and H. Jiang, *Org. Biomol. Chem*., 2015, **13**, 1225.

9 (a) S. Bhunia, K.-C. Wang and R.-S. Liu, *Angew. Chem. Int. Ed*., 2008, **47**, 5063; (b) M. Terada, F. Li, and Y. Toda, *Angew. Chem. Int. Ed*., 2014, **53**, 235; (c) S. M. Inamdar A. Konala and N. T. Patil, *Chem. Commun*., 2014, **50**, 15124.

10 (a) L. Overma, *Acc. Chem. Res*., 1992, **25**, 352; (b) S. R. Crosby, J. R. Harding, C. D. King, G. D. Parker and C. L. Willis, *Org. Lett*., 2002, **4**, 3407; (c) S. R. Crosby, J. R. Harding, C. D. King, G. D. Parker and C. L. Willis, *Org. Lett*., 2002, **4**, 577; (d) D. L. Aubele, C. A. Lee and P. E. Floreancig, *Org. Lett*., 2003, **5**, 4521; (e) Y. S. Cho, K. Karupaiyan, H. J. Kang, A. N. Pae, J. H. Cha, H. Y. Koh and M. H. Chang, *Chem. Commun*., 2003, 2346; (f) R. Jasti and S. D. Rychnovsky, *J. Am. Chem. Soc*., 2006, **128**, 13640; (g) A. C. Spivey, L. Laraia, A. R. Bayly, H. S. Rzepa and A. J. P. White, *Org. Lett*., 2010, **12**, 900; (h) P. Borkar, P. Weghe, B. V. S. Reddy, J. S. Yadav and R. Gree, *Chem. Commun*., 2012, **48**, 9316; (i) C. Lalli and P. Weghe, *Chem. Commun*., 2014, **50**, 7495.

11 (a) P. K. Sasmal and M. E. Maier, *Org. Lett*., 2002, **4**, 1271; (b) S. P. Fearnley and P. Lory, *Org. Lett*., 2007, **9**, 3507.

12 (a) F. P. Marmsater and F. G. West, *J. Am. Chem. Soc*., 2001, **123**, 5144; (b) J. S. Clark, T. C. Fessard and C. Wilson, *Org. Lett*., 2004, **6**, 1773; (c) D. M. Jaber, R. N. Burgin, M. Hepler, P. Zavalij and M. P. Doyle, *Chem. Commun*., 2011, **47**, 7623.

13 (a) B. Wunsch, M. Zott and G.Hofner, *Arch. Pharm*., 1992, **325**, 733; (b) B. Wunsch, M. Zott and G. Hofner, *Arch. Pharm*., 1993, **326**, 823; (c) R. Dupont, L. Jeanson, J.-F. Mouscadet and P. Cotelle, *Bioorg. Med. Chem. Lett*., 2001, **11**, 3175; (d) C. Maurin, F. Bailly and P. Cortelle, *Curr. Med. Chem*., 2003, **10**, 1795.

14 (a) I. V. Alabugin, K. Gilmore and M. Manoharan, *J. Am. Chem. Soc*., 2011, **133**, 12608; (b) K. Gilmore and I. V. Alabugin, *Chem. Rev*., 2011, **111**, 6513.

15 CCDC 1057787-1057790 (**6d**, **7d, 7i** and **7m**) contains the supplementary crystallographic data for this paper.

