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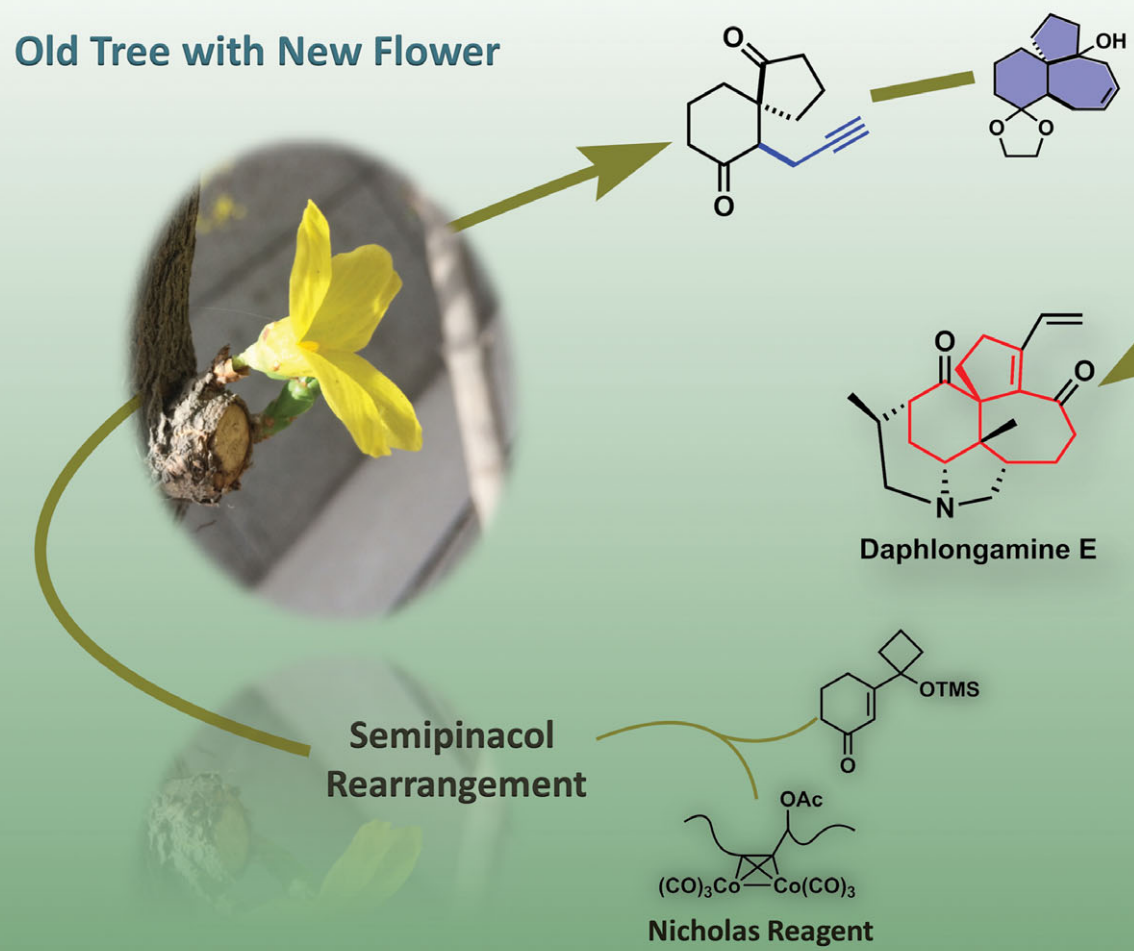

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Propargylic cation-induced intermolecular electrophilic addition–semipinacol rearrangement†

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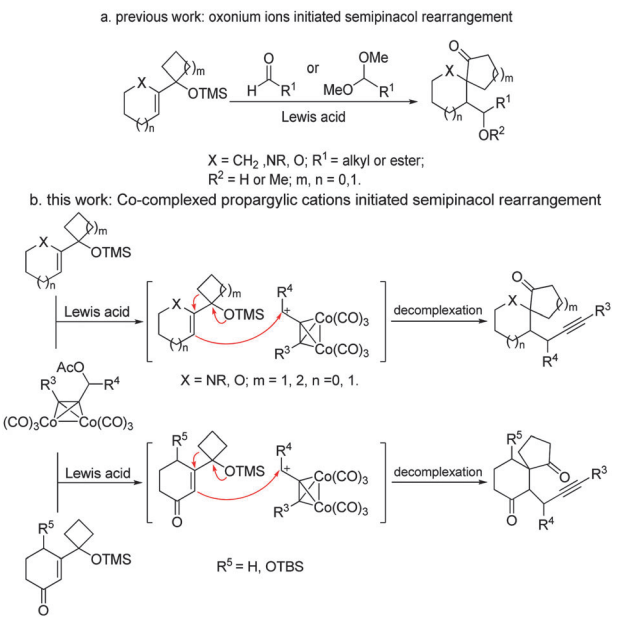
A novel propargylic electrophile-induced tandem intermolecular addition–semipinacol rearrangement was developed efficiently under mild conditions. Various allylic silylether substrates as well as Co-complexed propargylic species were applicable to this protocol and gave a series of synthetically useful β-propargyl spirocyclic ketones in moderate to good yields. Its synthetic application was also demonstrated by an efficient construction of the key tricyclic moiety of daphlongamine E.

As one of the most powerful methods for C–C bond formation and reorganization, the electrophilic addition–semipinacol rearrangement of allylic alcohol has been extensively utilized in organic synthesis.[1] Accordingly, lots of electrophiles have been explored for achieving different synthetic goals *via* this rearrangement, but most of them belong to non-carbon species,[1b–d] such as protons, halogens and some other heteroatom-containing species. In fact, carbon electrophile-initiated rearrangements could generate more complex and diverse carbon skeletons of the resulting molecules if the electrophilic addition step could be realized, and thus would play a much more important role in the synthesis of complex architectures. However, it was not until 1969 that an intramolecular acetal-participating semipinacol rearrangement (also known as the Prins-pinacol reaction) was explored.[2a,b] Later this reaction was further extended and used as a key step in a number of synthetic approaches.[1a,2] In contrast, intermolecular carbon electrophile-initiated rearrangements have been largely underexplored in comparison with intramolecular versions, despite them being more powerful and versatile than the latter, in view of the complexity and diversity of carbon frameworks generated.[3] In 2007, Cha's group reported a hemiacetal-initiated intermolecular reaction,[3a] which was well used in the total synthesis of cyathin A_3 and B_2.[3b] Later in 2010, Aubé's group further extended this method to accomplish the synthesis of lepadiformines.[3c] Recently, our group has also reported that an activated aldehyde carbonyl group of ethyl glyoxalate ester could trigger a reaction with dihydropyran-type allylic silylethers under catalysis by Cu(II), providing various tricyclic systems in high efficiency.[3e] In spite of these pioneering works mentioned above, the carbon electrophiles used in these intermolecular reactions are only confined to oxonium ions derived from acetal or aldehyde (Scheme 1a). Therefore, exploring multi-functionalizable electrophiles and further developing synthetically more versatile intermolecular carbon-electrophile-initiated semipinacol rearrangements are still in high demand for organic synthesis.

The challenge for developing this kind of intermolecular reaction lies in not only finding suitable conditions to generate a carbenium ion electrophile active enough to take part in an



Scheme 1 Design of the carbon electrophile-initiated semipinacol rearrangement.

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† Electronic supplementary information (ESI) available. CCDC 973585 (**3j**), 973583 (**3n**) and 973584 (**6a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc49650c

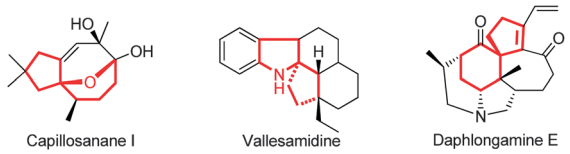


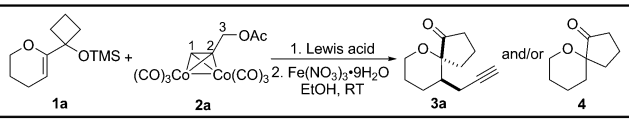
Fig. 1 Natural products containing various spirocyclic units.

intermolecular addition to the allylic alcohol or its silylether, but it also requires that the substrate survives self-rearrangement under these conditions. In this regard and in consideration of the multi-reactivity and broad synthesis of the propargylic electrophiles generated from Nicholas Co-complexed propargylic species,[4,5] we envisioned that this *in situ* generated cation would be a sufficiently active electrophile[6] to promote such an intermolecular reaction (Scheme 1b). Herein, we wish to present our preliminary research results on this tandem propargylation–semipinacol reaction, which has provided a series of α-quaternary β-propargyl spirocyclic ketones and established a short route to the formation of the 5/6/7-tricyclic core of daphlongamine E.

As spirocyclic units possessing oxa-, aza- and all-carbon-quaternary centers are present in numerous bioactive natural products, for example capillosanane, vallesamidine and daphlongamine (Fig. 1), the allylic silylether substrates with the corresponding dihydropyran,[3e,7a] dihydropyrrole[7b] and cycloalkenone[7c,d] motifs, which can be readily prepared from commercially available materials in short steps, were used to examine our predicted tandem reaction for constructing these units. Firstly, the dihydropyran-type allylic silylether **1a** and the Ac-protected Co-complexed propargylic species **2a** were used as model substrates to screen the reaction conditions (Table 1). Initially, several Lewis acids ($BF_3{\cdot}Et_2O$, $In(OTf)_3$, $EtAlCl_2$ and $AlCl_3$) were tested in dichloromethane (DCM). Unfortunately, the reactions always resulted in a single undesired self-rearrangement product **4** in high yield, except when using $AlCl_3$ (entry 1)[8] in which the desired product **3a** could be produced in low total yield of 32% after subsequent demetalation of the Co-complexed-product with $Fe(NO_3)_3{\cdot}9H_2O$. Considering that the competing self-rearrangement might take place prior to the formation of the Co-complexed propargylic cation under promotion by Lewis acids, we altered our experimental sequence.[9] Thus, the mixture of $AlCl_3$ and **2a** in DCM was first stirred at 0 °C for 1.5 hours, then a solution of **1a** in DCM was added at −78 °C. To our delight, this operation improved the yield to 43% (entry 2). Then, more Lewis acids were screened to further optimize this reaction. In the presence of $In(OTf)_3$ or $SnBr_4$, only the undesired ketone **4** was obtained (entries 3 and 4). Other Lewis acids, such as $EtAlCl_2$, $BF_3{\cdot}Et_2O$, and $TiCl_4$, were effective, but also could not completely avoid the formation of **4** (entries 5–7). Fortunately, a good overall yield of 71% was achieved when $SnCl_4$ was used, and only trace amounts of **4** were obtained (entry 8). Furthermore, solvent effects were also observed in this tandem process. When toluene was used, the reaction yield decreased dramatically to 42% (entry 9). While the use of some other solvents containing O- or N-atoms (such as acetone, acetonitrile, THF, or DME) afforded much poorer results, leading to only **4** or no reaction.

Under the specified optimized conditions (Table 1, entry 8, for a detailed description see also ref. 9) we then probed the scope of the substrate in this transformation (Table 2). First, a range of active dihydropyran-type allylic silylethers **1a–1f** was subjected to the standard reaction conditions. Among them, **1b–1d** with aryl or alkyl substituents on the cyclobutane moiety went smoothly through the rearrangement initiated by the unsubstituted Co-complexed propargyl electrophile, giving the corresponding spirocyclic ketones **3b–3d** in moderate to good yields (65–75%). A larger-sized cyclopentanol silylether **1e** was also effective for this rearrangement, albeit in a slightly lower yield (57%). This protocol could be further extended to the secondary alcohol silylether **1f**, but the yield of **3f** formed was much lower (31%), which might be due to the partial decomposition of Co-complexed **3f** in the acidic environment. Next, various substituted

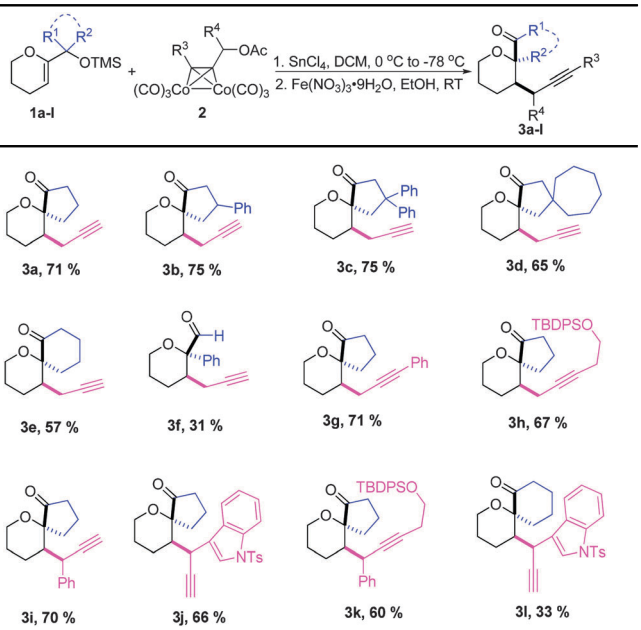
Table 1 Optimization of Co-complexed propargyl electrophile initiated semipinacol rearrangement[a]



Entry	Lewis acid	Solvent	Time (min)	Yield of **3a**[b] (%)	Yield of **4**[b] (%)
1[c]	$AlCl_3$	DCM	90	32	23
2[c]	$AlCl_3$	DCM	90	43	40
3[c]	$In(OTf)_3$	DCM	90	None	70
4	$SnBr_4$	DCM	45	None	42
5	$EtAlCl_2$	DCM	10	23	66
6	$BF_3{\cdot}Et_2O$	DCM	10	37	37
7	$TiCl_4$	DCM	10	58	25
8	$SnCl_4$	DCM	10	71	Trace
9[c]	$SnCl_4$	Toluene	90	42	Trace

[a] Unless otherwise specified the reaction operated in a general process.[9] [b] Isolated yield. [c] Reaction performed at −78 °C to RT.

Table 2 Reaction results of dihydropyran-type allylic silylethers **1a–1l** with Co-complexed propargyl electrophiles



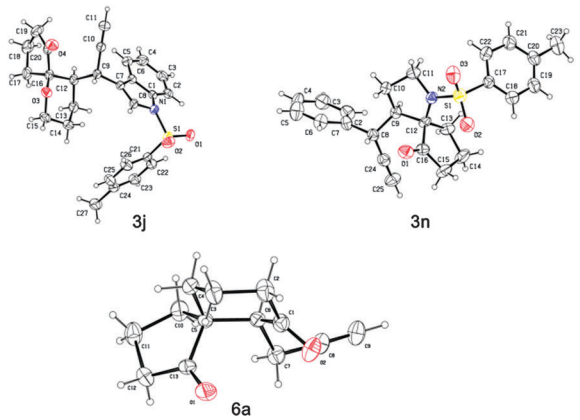


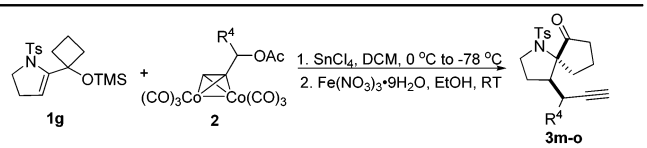
Fig. 2 X-ray crystal structures of **3j**, **3n** and **6a**.[13]

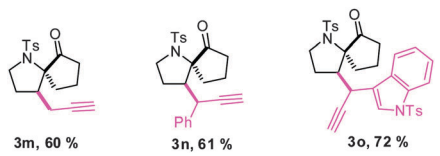
Co-complexed proparyl electrophiles were examined under the same conditions.[9] Fortunately, different substitutions at C1 and C3 of the Co-complexed propargyl electrophiles were well tolerated without significantly affecting the reaction efficiency, affording the corresponding products **3g–3l** in moderate to good yields in most cases. Additionally, the use of the 3,3-dimethyl-substituted Co-complexed propargyl electrophile only resulted in the self-rearrangement product, probably because the *in situ* formed cation underwent proton-elimination before electrophilic addition.[10] The *trans*-relative configurations between propargyl and the migrating carbon in the products **3a–3l** were deduced by X-ray diffraction of **3j** as a representative (Fig. 2), which was consistent with the stereoselectivity of a typical electrophilic addition–semipinacol rearrangement.[11]

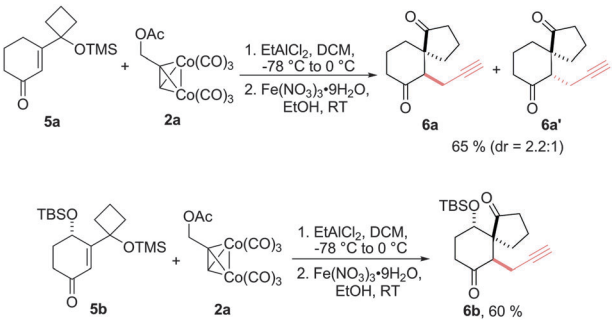
Subsequently, the dihydropyrrole-type allylic silylether **1g** was examined and demonstrated to be well effective to several Co-complexed propargylic electrophiles under standard conditions,[9] producing **3m**, **3n**, and **3o** in good yields (Table 3). The relative configuration of **3m–o** was deduced by X-ray diffraction of **3n** (Fig. 2).

Having obtained the results above, we then attempted to further extend the substrate scope to cyclohexenone-type allylic silylethers **5a** and **5b**. Frustratingly, when substrate **5a** was subjected to the above reaction conditions,[9] only trace amounts of desired product were observed. Considering that $SnCl_4$ might be ineffective for these types of substrates, we re-screened the Lewis acids and found that $EtAlCl_2$ was the best choice for promoting this reaction.[12] Consequently, separable spirocyclic diones **6a** and **6a′** were obtained in 65% overall yield with the diastereoselectivity 2.2 : 1. The configuration of the major diastereomer **6a** was also unambiguously confirmed by single crystal X-ray analysis (Fig. 2). To our delight, **5b** could provide **6b** as a single diastereomer under the same conditions, indicating that a bulky C4-substituent at the cyclohexenone ring could control well the diastereoselectivity of this reaction (Scheme 2).

Table 3 Reaction results of dihydropyrrole-type allylic silylether **1g** with Co-complexed propargyl electrophiles



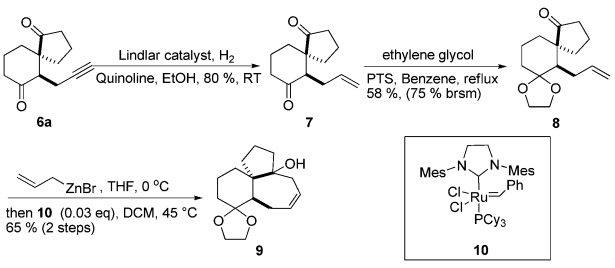




Scheme 2 Reaction results of the cyclohexenone-type allylic silylethers **5a** and **5b** with Co-complexed propargyl electrophiles.

After realizing the tandem Nicholas–semipinacol reaction on various types of allylic silylethers, we then focused our attention on its synthetic applications. In connection with our research interest in the total synthesis of daphlongamine E,[7d,14,15] we proposed that the propargyl group introduced in compound **6a** could be used to construct concisely the key and challenging all-carbon 5/6/7-tricyclic motif **9** of this type of alkaloid. As shown in Scheme 3, controlled hydrogenation of the triple bond of **6a** with Lindlar Pd afforded olefin **7** in 80% yield. Then, selective protection of the carbonyl group of the cyclohexenone moiety with ethylene glycol[16] generated compound **8**. Introduction of another allyl group to **8** with allylzinc bromide,[17] followed by a direct ring-close metathesis[18] with Grubbs II catalyst **10**, readily provided the 5/6/7-tricyclic structure **9** (65% yield in two steps).

In summary, we have successfully developed a Nicholas propargyl electrophile-induced tandem intermolecular semipinacol rearrangement, which is applicable to a wide range of allylic silylether substrates as well as Nicholas species, yielding a series of β-propargyl spirocyclic ketones in moderate to good yields. Its additional features include: good efficiency, high diastereoselectivity, mild reaction conditions, and easy handling. We believe this methodology must find good utility in the synthesis of polycyclic natural products such as daphlongamine E.



Scheme 3 Synthesis of the key 5/6/7-tricyclic unit of daphlongamine E.

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Notes and references

1 (*a*) B. B. Snider, in *The Prins Reaction and Carbonyl Ene Reactions*, ed. B. M. Trost, I. Fleming and C. H. Heathcock, Pergamon, New York, 1991, vol. 2, p. 527; (*b*) L. E. Overman, *Acc. Chem. Res.*, 1992, **25**, 352–359; (*c*) T. J. Snape, *Chem. Soc. Rev.*, 2007, **36**, 1823–1842; (*d*) E. Leemans, M. D'hooghe and N. De Kimpe, *Chem. Rev.*, 2011, **111**, 3268–3333; (*e*) Z.-L. Song, C.-A. Fan and Y.-Q. Tu, *Chem. Rev.*, 2011, **111**, 7523–7556; (*f*) B. Wang and Y.-Q. Tu, *Acc. Chem. Res.*, 2011, **44**, 1207–1222.

2 (*a*) P. Martinet, G. Mousset and M. Colineau, *C. R. Seances Acad. Sci., Ser. C*, 1969, **268**, 1303–1306; (*b*) P. Martinet and G. Mousset, *Bull. Soc. Chim. Fr.*, 1970, 1071–1076; (*c*) L. E. Overman and L. D. Pennington, *J. Org. Chem.*, 2003, **68**, 7143–7157; (*d*) L. Kürti and B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, Burlington, MA, 2005, pp. 366–367.

3 (*a*) I. L. Lysenko, H.-S. Oh and J. K. Cha, *J. Org. Chem.*, 2007, **72**, 7903–7908; (*b*) K. Kim and J. K. Cha, *Angew. Chem., Int. Ed.*, 2009, **48**, 5334–5336; (*c*) A. M. Meyer, C. E. Katz, S.-W. Li, D. Vander Velde and J. Aubé, *Org. Lett.*, 2010, **12**, 1244–1247; (*d*) R. J. Phipps, L. McMurray, S. Ritter, H. A. Duong and M. J. Gaunt, *J. Am. Chem. Soc.*, 2012, **134**, 10773–10776; (*e*) Q.-W. Zhang, X.-B. Zhang, B.-S. Li, K. Xiang, F.-M. Zhang, S.-H. Wang and Y.-Q. Tu, *Chem. Commun.*, 2013, **49**, 1648–1650; (*f*) X. Liu, F. Xiong, X. Huang, L. Xu, P. Li and X. Wu, *Angew. Chem., Int. Ed.*, 2013, **52**, 6962–6966; (*g*) Z.-M. Chen, W. Bai, S.-H. Wang, B.-M. Yang, Y.-Q. Tu and F.-M. Zhang, *Angew. Chem., Int. Ed.*, 2013, **52**, 9781–9785; (*h*) H. Egami, R. Shimizu, Y. Usui and M. Sodeoka, *Chem. Commun.*, 2013, **49**, 7346–7348.

4 For the application of alkyne and alkyne–cobalt complex: (*a*) B. Godoi, R. F. Schumacher and G. Zeni, *Chem. Rev.*, 2011, **111**, 2937–2980; (*b*) A. J. Fletcher and S. D. R. Christie, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1657–1668.

5 K. M. Nicholas and R. Pettit, *Tetrahedron Lett.*, 1971, **12**, 3475–3478.

6 For reviews of the Nicholas reaction, see: (*a*) K. M. Nicholas, *Acc. Chem. Res.*, 1987, **20**, 207–214; (*b*) A. J. M. Caffyn and K. M. Nicholas, in *Comprehensive Organometallic Chemistry II*, ed. E. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon, Kidlington, 1995, vol. 12, p. 703; (*c*) T. J. J. Müller, *Eur. J. Org. Chem.*, 2001, 2021–2033; (*d*) J. R. Green, *Curr. Org. Chem.*, 2001, **5**, 809–826; (*e*) M. E. Welker, *Curr. Org. Chem.*, 2001, **5**, 785–807; (*f*) B. J. Teobald, *Tetrahedron*, 2002, **58**, 4133–4170; (*g*) J. R. Green, *Eur. J. Org. Chem.*, 2008, 6053–6062; (*h*) N. Kann, *Curr. Org. Chem.*, 2012, **16**, 322–334; (*i*) J. R. Green, *Synlett*, 2012, **23**, 1271–1282. Selected examples on Nicholas reaction, see; (*j*) T. Nakamura, T. Matsui, K. Tanino and I. Kuwajima, *J. Org. Chem.*, 1997, **62**, 3032–3033; (*k*) F. R. P. Crisóstomo, T. Martín and V. S. Martín, *Org. Lett.*, 2004, **6**, 565–568; (*l*) M. M. Quintal, K. D. Closser and K. M. Shea, *Org. Lett.*, 2004, **6**, 4949–4952; (*m*) K. M. Shea, K. D. Closser and M. M. Quintal, *J. Org. Chem.*, 2005, **70**, 9088–9091; (*n*) E. Álvaro, M. C. de la Torre and M. A. Sierra, *Chem.–Eur. J.*, 2006, **12**, 6403–6411; (*o*) N. Ortega, T. Martín and V. S. Martín, *Org. Lett.*, 2006, **8**, 871–873; (*p*) J. N. Hernández, M. A. Ramírez, M. L. Rodríguez and V. S. Martín, *Org. Lett.*, 2008, **10**, 2349–2352; (*q*) J. H. Kaldis, M. A. Brook and M. J. McGlinchey, *Chem.–Eur. J.*, 2008, **14**, 10074–10084; (*r*) C. Olier, N. Azzi, G. Gil, S. Gastaldi and M. P. Bertrand, *J. Org. Chem.*, 2008, **73**, 8469–8473; (*s*) K. D. Closser, M. M. Quintal and K. M. Shea, *J. Org. Chem.*, 2009, **74**, 3680–3688; (*t*) N. Kihara and K. Kidoba, *Org. Lett.*, 2009, **11**, 1313–1316; (*u*) A. M. Gómez, F. Lobo, D. Pérez de las Vacas, S. Valverde and J. C. López, *Chem. Commun.*, 2010, **46**, 6159–6161; (*v*) S. Djurdjevic, F. Yang and J. R. Green, *J. Org. Chem.*, 2010, **75**, 8241–8251; (*w*) K. Mitachi, T. Shimizu, M. Miyashita and K. Tanino, *Tetrahedron Lett.*, 2010, **51**, 3983–3986; (*x*) N. Ortega, V. S. Martín and T. Martín, *J. Org. Chem.*, 2010, **75**, 6660–6672; (*y*) R. A. Taj and J. R. Green, *J. Org. Chem.*, 2010, **75**, 8258–8270; (*z*) S. Amiralaei, J. Gauld and J. R. Green, *Chem.–Eur. J.*, 2011, **17**, 4157–4165; (*aa*) M. E. Krafft, M. J. Campbell, S. Kerrigan and J. W. Cran, *Tetrahedron Lett.*, 2011, **52**, 1090–1092; (*ab*) P. Brawn, E. Tyrrell, M. Carew, K. H. Tesfa and I. Greenwood, *Tetrahedron*, 2012, **68**, 10040–10048; (*ac*) Y. Nishibayashi, *Synthesis*, 2012, 489–503; (*ad*) E. Tyrrell, K. Mazloumi, D. Banti, P. Sajdak, A. Sinclair and A. Le Gresley, *Tetrahedron Lett.*, 2012, **53**, 4280–4282; (*ae*) D. Valette, Y. Lian, J. P. Haydek, K. I. Hardcastle and H. M. L. Davies, *Angew. Chem.*, 2012, **124**, 8764–8767; (*af*) S. Djurdjevic and J. R. Green, *Org. Lett.*, 2013, **15**, 5468–5471; (*ag*) C. Mukai, T. Kojima, T. Kawamura and F. Inagaki, *Tetrahedron*, 2013, **69**, 7659–7669; (*ah*) J. Rodríguez-López, F. Pinacho Crisóstomo, N. Ortega, M. López-Rodríguez, V. S. Martín and T. Martín, *Angew. Chem., Int. Ed.*, 2013, **52**, 3659–3662.

7 (*a*) Q.-W. Zhang, C.-A. Fan, H.-J. Zhang, Y.-Q. Tu, Y.-M. Zhao, P. Gu and Z.-M. Chen, *Angew. Chem., Int. Ed.*, 2009, **48**, 8572–8574; (*b*) Q.-W. Zhang, K. Xiang, Y.-Q. Tu, S.-Y. Zhang, X.-M. Zhang, Y.-M. Zhao and T.-C. Zhang, *Chem.–Asian J.*, 2012, **7**, 894–898; (*c*) E. Zhang, C.-A. Fan, Y.-Q. Tu, F.-M. Zhang and Y.-L. Song, *J. Am. Chem. Soc.*, 2009, **131**, 14626–14627; (*d*) M. Yang, L. Wang, Z.-H. He, S.-H. Wang, S.-Y. Zhang, Y.-Q. Tu and F.-M. Zhang, *Org. Lett.*, 2012, **14**, 5114–5117.

8 Initial reaction conditions: $AlCl_3$ (32 mg, 0.24 mmol) was added to the mixture of **1a** (50 mg, 0.22 mmol) and cobalt complex **2a** (crude, 93 mg, about 0.24 mmol) in DCM (3.6 mL) at −78 °C.

9 For the experimental details see the ESI†.

10 M. Nakagawa, J. Ma and T. Hino, *Heterocycles*, 1990, **30**, 451–462.

11 The detailed mechanism is demonstrated in the ESI†.

12 For the experimental details see the ESI†.

13 X-ray structures of **3j**, **3n** and **6a** with thermal ellipsoids drawn at 30% probability level, CCDC 973585 (**3j**), CCDC 973583 (**3n**), CCDC 973584 (**6a**).

14 For the isolation of Calyciphylline A-type alkaloids, see: J. Kobayashi and T. Kubota, *Nat. Prod. Rep.*, 2009, **26**, 936–962.

15 For the recent synthetic approaches to Calyciphylline A-type alkaloids, see: (*a*) D. Solé, X. Urbaneja and J. Bonjoch, *Org. Lett.*, 2005, **7**, 5461–5464; (*b*) A. Cordero-Vargas, X. Urbaneja and J. Bonjoch, *Synlett*, 2007, 2379–2382; (*c*) C. Xu, Z. Liu, H. Wang, B. Zhang, Z. Xiang, X. Hao and D. Z. Wang, *Org. Lett.*, 2011, **13**, 1812–1815; (*d*) F. Sladojevich, I. N. Michaelides, D. Benjamin, J. W. Ward and D. J. Dixon, *Org. Lett.*, 2011, **13**, 5132–5135; (*e*) C. Xu, L. Wang, X. Hao and D. Z. Wang, *J. Org. Chem.*, 2012, **77**, 6307–6313; (*f*) Y. Yao and G. Liang, *Org. Lett.*, 2012, **14**, 5499–5501.

16 S.-H. Hou, Y.-Q. Tu, L. Liu, F.-M. Zhang, S.-H. Wang and X.-M. Zhang, *Angew. Chem., Int. Ed.*, 2013, **52**, 11373–11376.

17 F. Grepioni and D. Savoia, *J. Org. Chem.*, 1997, **62**, 4180–4182.

18 K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4490–4527.

