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Facile access to diverse all-carbon quaternary center containing spirobicycles by exploring a tandem Castro–Stephens coupling/acyloxy shift/cyclization/semipinacol rearrangement sequence†

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Efficient combination of two or more reactions into a practically useful purification free sequence is of great significance for the achievement of structural complexity and diversity, and an important approach for the development of new synthetic strategies that are industrially step-economic and environmentally friendly. In this work, a facile and efficient method for the construction of highly functionalized spirocyclo[4.5]decane derivatives containing a synthetically challenging quaternary carbon center has been successfully developed through the realization of a tandem Castro–Stephens coupling/1,3-acyloxy shift/cyclization/semipinacol rearrangement sequence. Thus a series of multi-substituted spirocyclo[4.5]decane and functionalized cyclohexane skeletons with a phenyl-substituted quaternary carbon center have been constructed using this method as illustrated by 24 examples in moderate to good yields. The major advantages of this method over the known strategies are better transformation efficiency (four consecutive transformations in one tandem reaction), product complexity and diversity. As a support of its potential application, a quick construction of the key tetracyclic diterpene skeleton of waihoensene has been achieved.

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Introduction

Spiro bicyclic scaffolds incorporating all-carbon quaternary stereocenters, as a big number of key structural moieties, broadly exist in bioactive natural products and pharmaceutical molecules, and often play essential roles in their characteristic bioactivity.¹ Because of the highly steric repulsion caused by its four carbonic substituents,² however, the construction of this type of moiety is a long-standing challenging topic.³ Taking the spirocyclo[4.5]decane skeleton as a typical example, a lot of bioactive natural products as well as synthetic intermediates contain this key unit (Fig. 1).⁴ Therefore, in order to synthesize these target molecules and facilitate corresponding molecular function studies, how to efficiently construct this unit has

become a crucial and difficult step. Although several strategies based on different intermolecular or intramolecular cycloaddition patterns of relatively complex substrates have been developed during the past decade,⁵ it is still highly desirable to further explore alternative approaches for pursuing transformation efficiency, and product diversity as well as extensibility.

Results

Design plan

Besides the above strategies, it is particularly noticeable that the semipinacol rearrangement reaction, which can generate

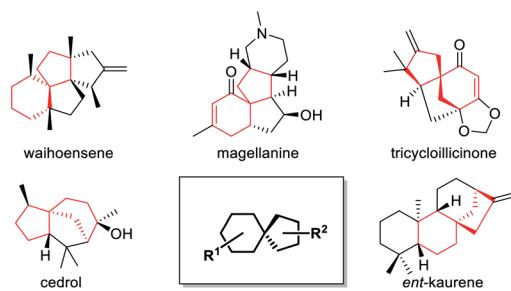


Fig. 1 Representative important natural products bearing the spirocyclo[4.5]decane core.

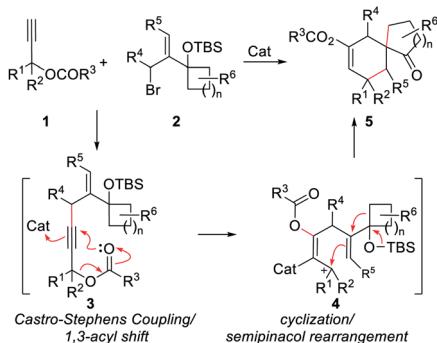
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Current work: four conversions in one tandem process



Scheme 1 Strategy design toward the spirocyclo[4.5]decane skeleton.

a spirocyclic quaternary carbon center through functional group migration or skeleton reorganization, has been used by us⁶ and several other research groups⁷ for the syntheses of a variety of bioactive molecules containing spirocyclo[4.5] decane and related skeletons. Accordingly, the development of more efficient semipinacol rearrangement involved reaction patterns is always a main research program of our group, especially, through ingenious design and realization of sequential chemical transformations in step economy. Inspired by the special chemical properties of propargyl ester in acyloxy shift/cyclizations,⁸ we envisioned that a 1,3-acyloxy shift of the propargyl ester⁹ intermediate 3 generated by a Castro-Stephens coupling¹⁰ from propargyl ester 1 and allylic bromide 2 possessing a potential migration moiety might be viable to trigger a cyclization/semipinacol rearrangement of 4 affording multi-substituted spirocyclo[4.5]decane and related skeletons (Scheme 1). Based on the mechanism analysis of the above four transformations, it is highly likely to achieve them in a tandem manner. Additionally, since a series of substituent combinations can be used from the two substrates, this strategy, once feasible, will not only exhibit better transformation efficiency and product complexity and diversity, but also further enrich the content of semipinacol rearrangement. Herein, we present such a novel sequence and its application in the construction of the tetracyclic ring system of waihoensene, a new example of complex bioactive molecule-directed synthetic methodology development.

Discussion

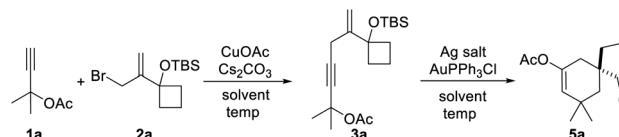
Optimization of reaction conditions

Following the above assumption, we first tested the feasibility of the designed tandem reaction using propargyl ester 1a and allylic bromide 2a as the model substrates. As the copper catalyst has been successfully applied in Castro-Stephens coupling and the 1,3-acyloxy shift process to form an allene group,¹¹ different copper catalysts were examined for promoting the expected reaction.¹² Although none of them afforded the desired final product 5a, most could give the Castro-Stephens coupling product 3a, with a best yield of 68% using CuOAc.¹² Further screening of the base additive, solvent and reaction temperature

showed that the use of Cs₂CO₃ in DCE at 70 °C could produce 3a in the best yield of 82% (Table 1, entry 1). Subsequently, the realization of the initial tandem reaction in a purification free manner was then investigated. Fortunately, after a quick removal of the solid from the reaction mixture through Celite pad filtration following the Castro-Stephens coupling reaction, a first attempt using the combination of 10 mol% AuPPh₃Cl and AgOTf could promote the desired reaction to give the product 5a in 57% yield (Table 1, entry 7). Furthermore, the counterion effect¹³ was also observed with this reaction, and the use of counterion NTF₂⁻ from AgNTF₂ exhibited the best result of 66% yield for 5a (Table 1, entry 8). Next, several different solvents were applied to this tandem reaction. Among them, benzene, THF and CH₃CN could give the desired product in low yield (Table 1, entries 11–16). Other solvents were not compatible with this transformation. Finally, the use of CuOAc along with Cs₂CO₃ and the combination of AuPPh₃Cl and AgNTF₂ in DCE (Table 1, entry 8) was selected as the optimal reaction conditions.

Substrate scope investigation

With the optimal reaction conditions in hand (Table 1, entry 8), we began to explore the generality of this reaction, and the results are summarized in Tables 2 and 3. Among the substrates tested,

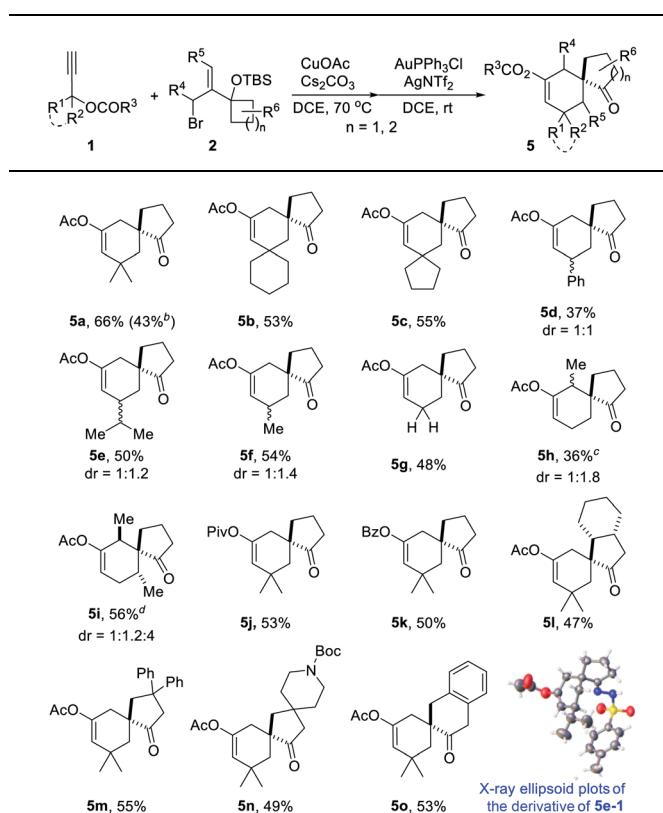
Table 1 Optimization of reaction conditions^a

Entry	Solvent	Ag salt	Temp	Product	Yield
1	DCE ^b	—	70 °C ^c	3a	82% ^d
2	Benzene ^b	—	rt ^c	3a	40% ^d
3	THF ^b	—	rt ^c	3a	47% ^d
4	EtOH ^b	—	rt ^c	3a	55% ^d
5	CH ₃ CN ^b	—	rt ^c	3a	55% ^d
6	DMF ^b	—	rt ^c	3a	54% ^d
7	DCE	AgOTf	rt ^e	5a	57% ^f
8	DCE	AgNTF ₂	rt ^e	5a	66% ^f
9	DCE	AgSbF ₆	rt ^e	5a	53% ^f
10	DCE	AgBF ₄	rt ^e	5a	49% ^f
11	Benzene ^g	AgNTF ₂	rt ^e	5a	11% ^f
12	THF ^g	AgNTF ₂	rt ^e	5a	27% ^f
13	EtOH ^g	AgNTF ₂	rt ^e	5a	nd
14	CH ₃ CN ^g	AgNTF ₂	rt ^e	5a	53% ^f
15	DMF ^g	AgNTF ₂	rt ^e	5a	nd
16	DMSO ^g	AgNTF ₂	rt ^e	5a	nd

^a Unless specified, all reactions were carried out using 1a (0.5 mmol, 2.5 eq.), 2a (0.2 mmol, 1.0 eq.), CuOAc (30 mol%), Cs₂CO₃ (50 mol%), AuPPh₃Cl (10 mol%), and Ag salt (10 mol%) in a reaction tube in DCE (2 mL) at indicated temperature. ^b The solvent of Castro-Stephens coupling for 3a. ^c Temperature for the first coupling reaction.

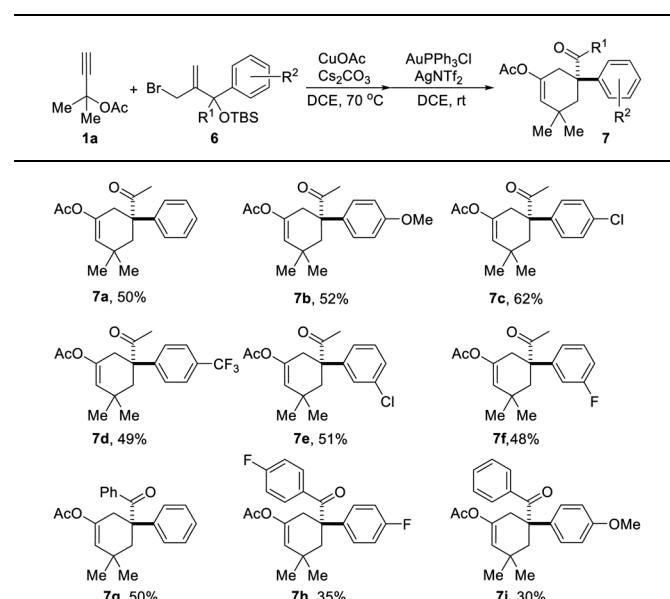
^d Isolated yield of 3a. ^e The first coupling step was carried out at 70 °C. ^f Isolated yield of 5a in a purification free manner. ^g After filtration, the filtrate was concentrated and diluted with the indicated solvent (4 mL) for the subsequent operation.



Table 2 Exploration of the generality of the tandem reaction of cyclic alkanes as migrating groups^a

^a Unless specified, all reactions were conducted using **1** (0.5 mmol, 2.5 eq.), **2** (0.2 mmol, 1.0 eq.), CuOAc (30 mol%), Cs_2CO_3 (50 mol%), AuPPh_3Cl (10 mol%), and AgNTf_2 (10 mol%) in a reaction tube in DCE (2 mL) at indicated temperature. ^b 10 mmol of **1a** (1.26 g) and 4 mmol of **2a** (1.22 g) were used. ^c CHCl_3 was used as the solvent after Castro–Stephens coupling. ^d AuCl_3 (10 mol%) in 2 mL HFB (hexafluorobenzene) was used instead of the combination of AuPPh_3Cl and AgNTf_2 after Castro–Stephens coupling; the structure shows the relative configuration of the major isomer.

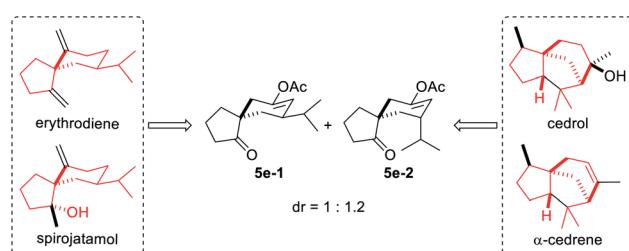
most of them could give the expected products in moderate to good yields. When R^1 and R^2 groups of propargyl ester formed a ring system (*i.e.*, cyclohexyl and cyclopentyl), the reaction with bromide **2a** ($\text{R}^4, \text{R}^5, \text{R}^6 = \text{H}$) proceeded smoothly providing tricyclic products **5b** and **5c** in 53% and 55% yield, respectively. Moreover, with the R^1 as H , R^2 could be H , Ph , isopropyl, or methyl, and all reactions could give the desired products **5d** to **5g** in moderate to good yields, albeit with low diastereoselectivity for **5d** to **5f**. Additionally, the reaction was also compatible with substrate **2** with different R^4/R^5 groups. In the case of substrate **2b** with R^4 and R^5 being Me and H, respectively, the expected product **5h** was obtained in 36% yield and 1/1 dr ratio. When both R^4 and R^5 were Me (**2c**), the desired product **5i** was produced with good diastereoselectivity and yield. It should be noted that a series of natural product skeletons might be obtained by our protocol. For example, since the relative configuration of the two diastereoisomers of ketone **5e** (ref. 14) (**5e-1** and **5e-2**) is consistent with natural products erythrodiene^{a,c,d} and cedrol,^{a,g,h} respectively, a new general synthetic strategy for these types of natural products might be developed based on propargyl ester with

Table 3 Exploration of the generality of the tandem reaction of aromatic rings as migrating groups^a

^a All reactions were conducted using **1a** (0.5 mmol, 2.5 eq.), **6** (0.2 mmol, 1.0 eq.), CuOAc (30 mol%), Cs_2CO_3 (50 mol%), AuPPh_3Cl (10 mol%), and AgNTf_2 (10 mol%) in a reaction tube in DCE (2 mL) at indicated temperature.

pivaloyl, and benzoyl was successful to give the corresponding products **5j** and **5k** in 53% and 50% yield, respectively. In order to prove the efficiency of this method in the rapid construction of product complexity, other four allylic bromides **2d**–**2g** were applied to the reaction, which produced four spirocyclic products in good yields. Among them, products **5l** and **5m** confirmed the feasibility of adding additional substituents on the cyclobutanol moiety, while product **5n** showed that the amine group is amenable to this reaction. It was noteworthy that substrate **2g** with a 2,3-dihydro-1*H*-inden-2-ol motif could go through the reaction through a five-membered ring to a six-membered ring expansion affording product **5o**. In order to demonstrate the potential utility of such a reaction, the transformation between **1a** and **2a** was attempted on the gram scale giving **5a** in a moderate yield of 43% (Scheme 2).

Based on the above results, the application of this method in the construction of a functionalized cyclohexane skeleton with a phenyl-substituted quaternary carbon center, a common



Scheme 2 New synthetic strategy design toward corresponding sesquiterpenes.



moiety in a variety of natural products like limaspermidine^{15a} and strychnine,^{15b} was further investigated. Accordingly, a series of allylic bromides with an aryl substituted tertiary alcohol moiety were applied to this reaction with substrate **1a**. All of the tested substrates afforded the expected products, and the regioselectivity of this reaction during the migration step agrees well with the common semipinacol rearrangement pattern, *i.e.*, aryl groups and aryl groups with an electron-donating substituent are more preferred than alkyl groups and aryl groups with an electron-withdrawing substituent, respectively. For example, substrates **6a–6f** all gave the aryl group migrated products, and substrate **6i** led to ketone **7i** as the sole product. Besides, the steric hindrance effect of the substituent on the aromatic ring has also been clearly observed. When the substituent on the phenyl ring was chloro, product **7c** with the substituent at the *para*-position was obtained in higher yield than the one with it at the *meta*-position (**7e**).

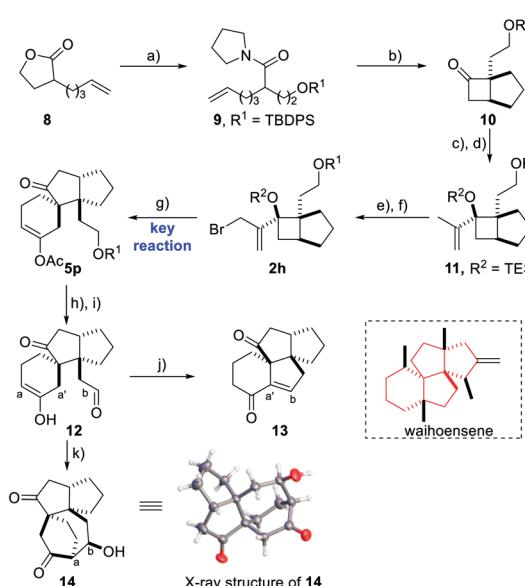
Synthetic application

In order to demonstrate the efficiency of this method in constructing a highly complex structural skeleton, a quick assembly of the key tetracyclic skeleton of waihoensene,¹⁶ a unique diterpene molecule isolated from the New Zealand podocarp, featuring fused and strained tetracyclic rings and four

consecutive congested all-carbon quaternary centers, was attempted using this reaction as the key step (Scheme 3). Due to the great difficulty in constructing such a tetracyclic framework with vicinal quaternary carbon centers, only one synthetic strategy toward waihoensene has been reported in 2017 using a tandem cycloaddition reaction of an allene substrate prepared in 12 steps as the key step.¹⁷ Herein, based on the method we developed, starting from prop-2-yn-1-yl acetate **1g** and **2h** synthesized from the known reagent **8** in 6 steps, a facile access to a tricyclic skeleton was accomplished affording **5p** in 40% yield and a dr ratio of 3.2/1 using hexafluorobenzene as the solvent.¹⁸ The relative configuration of **5p** and its diastereoisomer **5q** was confirmed by the X-ray structure analysis of their derivatives.¹⁴ Next, the TBDS protecting group of **5p** was removed with TBAF followed by IBX oxidation providing dicarbonyl compound **12**. A K_2CO_3 -induced tandem hydrolysis/intramolecular aldol cyclization/elimination reaction would give compound **13**. Thus a quick construction of the tetracyclic skeleton core of waihoensene with vicinal all-carbon centers was realized through the use of this key methodology. Additionally, an unprecedented [3.2.2] bridged motif **14** could be obtained through a different cyclization model in the presence of HCl.

Conclusions

In summary, targeting a highly functionalized spirocyclo[4.5] decane skeleton, a purification free tandem Castro–Stephens coupling/1,3-acyloxy shift/cyclization/semipinacol rearrangement reaction of propargyl esters with allylic bromide has been successfully developed. This method not only features a highly efficient chemical conversion into complex spirobicyclic compounds from simple readily available substrates, but also exhibits a wide substrate scope. Especially, compared with our previous work on semipinacol rearrangement related synthetic methodology, some characteristic functional groups that are necessary for the corresponding bioactive natural products, such as isopropyl^{14g,h} and geminal methyl groups,^{4a} can be readily installed. Moreover, the generation of a vinyl ester moiety by this transformation provides an important hinge for subsequent transformation enabling a quick construction of the key 6/5/5-fused tetracyclic skeleton of waihoensene. Further application of this method for the total synthesis of related bioactive natural products is ongoing in the same lab.



Scheme 3 Synthetic utility of the tetracyclic skeleton of waihoensene. Reagents and conditions: (a) pyrrolidine, Et_3N , neat, $85\text{ }^\circ C$, then $TBDPSiCl$, imidazole, CH_2Cl_2 , $0\text{ }^\circ C$ (98%); (b) Tf_2O , 2,6-di-*tert*-butyl-4-methylpyridine, DCE, reflux, then CCl_4/H_2O reflux (54%); (c) 2-bromopropene, $t\text{-}BuLi$, THF, $-78\text{ }^\circ C$ (85% brsm); (d) $TESOTf$, 2,6-lutidine, CH_2Cl_2 , $0\text{ }^\circ C$ (94%); (e) SeO_2 , TBHP, CH_2Cl_2 , $0\text{ }^\circ C$ – rt (73% brsm); (f) CBr_4 , PPh_3 , imidazole, CH_2Cl_2 , rt (90%); (g) prop-2-yn-1-yl acetate, $CuOAc$, Cs_2CO_3 , DCE, $70\text{ }^\circ C$, then $AuCl_3$, PTS, HFB (hexafluorobenzene), rt (40%, dr = 3.2 : 1); (h) TBAF, THF, $0\text{ }^\circ C$ (93%); (i) IBX, $EtOAc$, reflux (91%); (j) K_2CO_3 , $MeOH/H_2O$ = 100 : 1, $0\text{ }^\circ C$ – rt (64%); (k) HCl , THF , rt (89%). $TBDPSiCl$ = *tert*-butyl diphenylchlorosilane, DCE = 1,2-dichloroethane, $TESOTf$ = triethylsilyl trifluoromethanesulphonate, IBX = 2-iodoxybenzoic acid.

Conflicts of interest

The authors declare no competing interests.

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Notes and references

1 (a) P. Saraswat, G. Jeyabalan, M. Z. Hassan, M. U. Rahman and N. K. Nyola, Review of synthesis and various biological activities of spiro heterocyclic compounds comprising oxindole and pyrrolidine moieties, *Synth. Commun.*, 2016, **46**, 1643–1664; (b) Y. Ma and C. Fan, Progress in the synthesis of spirotryprostatin alkaloids, *Chin. J. Org. Chem.*, 2016, **36**, 2380–2396; (c) Y. Zheng, C. M. Tice and S. B. Singh, The use of spirocyclic scaffolds in drug discovery, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673–3682; (d) K. Ding, Z. Han and Z. Wang, Spiro skeletons: a class of privileged structure for chiral ligand design, *Chem.-Asian J.*, 2009, **4**, 32–41.

2 (a) S. Zhuo, T. Zhu, L. Zhou, C. Mou, H. Chai, Y. Lu, L. Pan, Z. Jin and Y. R. Chi, Access to all-carbon spirocycles through a carbene and thiourea cocatalytic desymmetrization cascade reaction, *Angew. Chem., Int. Ed.*, 2019, **58**, 1784–1788; (b) Y. Li and S. Xu, Transition-metal-catalyzed C–H functionalization for construction of quaternary carbon centers, *Chem.-Eur. J.*, 2018, **24**, 16218–16245; (c) S. Li, J. W. Zhang, X. L. Li, D. J. Cheng and B. Tan, Phosphoric acid-catalyzed asymmetric synthesis of SPINOL derivatives, *J. Am. Chem. Soc.*, 2016, **138**, 16561–16566; (d) B. F. Rahemtulla, H. F. Clark and M. D. Smith, Catalytic enantioselective synthesis of C₁- and C₂-symmetric spirobiindanones through counterion-directed enolate C-acylation, *Angew. Chem., Int. Ed.*, 2016, **55**, 13180–13183; (e) K. W. Quasdorf and L. E. Overman, Catalytic enantioselective synthesis of quaternary carbon stereocentres, *Nature*, 2014, **516**, 181–191; (f) A. Y. Hong and B. M. Stoltz, The construction of all-carbon quaternary stereocenters by use of Pd-catalyzed asymmetric allylic alkylation reactions in total synthesis, *Eur. J. Org. Chem.*, 2013, 2745–2759; (g) D. E. White, I. C. Stewart, R. H. Grubbs and B. M. Stoltz, The catalytic asymmetric total synthesis of elatol, *J. Am. Chem. Soc.*, 2008, **130**, 810–811.

3 For selected reviews: (a) P.-W. Xu, J.-S. Yu, C. Chen, Z.-Y. Cao, F. Zhou and J. Zhou, Catalytic enantioselective construction of spiro quaternary carbon stereocenters, *ACS Catal.*, 2019, **9**, 1820–1882; (b) A. Ding, M. Meazza, H. Guo, J. W. Yang and R. Rios, New development in the enantioselective synthesis of spiro compounds, *Chem. Soc. Rev.*, 2018, **47**, 5946–5996; (c) S. Kotha, N. R. Panguluri and R. Ali, Design and synthesis of spirocycles, *Eur. J. Org. Chem.*, 2017, 5316–5342; (d) L. K. Smith and I. R. Baxendale, Total syntheses of natural products containing spirocarbocycles, *Org. Biomol. Chem.*, 2015, **13**, 9907–9933; (e) A. D'Yakonov, V. O. A. Trapeznikova, A. de Meijere and U. M. Dzhemilev, Metal complex catalysis in the synthesis of spirocarbocycles, *Chem. Rev.*, 2014, **114**, 5775–5814; (f) K. Undheim, Preparation and structure classification of heteroaspiro [m.n] alkanes, *Synthesis*, 2014, **46**, 1957–2006; (g) R. Rios, Enantioselective methodologies for the synthesis of spiro compounds, *Chem. Soc. Rev.*, 2012, **41**, 1060–1074; (h) S. Kotha, A. Deb, K. Lahiri and E. Manivannan, Selected synthetic strategies to spirocyclics, *Synthesis*, 2009, 165–193.

4 (a) A. D. Rodríguez, C. Ramírez, I. I. Rodríguez and C. L. Barnes, Novel terpenoids from the West Indian sea whip *Pseudopterogorgia elisabethae* (Bayer). Elisapterosins A and B: Rearranged diterpenes possessing an unprecedented cagelike framework, *J. Org. Chem.*, 2000, **65**, 1390–1398; (b) D. B. Clarke, S. F. R. Hinkley and R. T. Weavers, Waihoensene. A new laurenene-related diterpene from *Podocarpus totara* var *waihoensis*, *Tetrahedron Lett.*, 1997, **38**, 4297–4300; (c) Y. Fukuyama, N. Shida, M. Kodama, H. Chaki and T. Yugami, Tticycloillicinone, a novel prenylated C₆–C₃ compound increasing choline acetyltransferase (ChAT) activity, isolated from *Illicium tashiroi*, *Chem. Pharm. Bull.*, 1995, **43**, 2270–2272; (d) C. Pathirana, W. Fenical, E. Corcoran and J. Clardy, Erythrodiene: a new spirobicyclic sesquiterpene of a rare skeletal class from the caribbean gorgonian coral *Erythropodium caribaeorum*, *Tetrahedron Lett.*, 1993, **34**, 3371–3372; (e) A. Bagchi, Y. Oshima and H. Hikino, Spirojatamol, a new skeletal sesquiterpenoid of *Nardostachys jatamansi* roots, *Tetrahedron*, 1990, **46**, 1523–1530; (f) P. Quitt, E. Mosettig, R. C. Cambie, P. S. Rutledge and L. H. Briggs, Optical rotatory dispersion studies. LVIII. 1. The complete absolute configurations of steviol, kaurene and the diterpene alkaloids of the garryfoline and atisine groups, *J. Am. Chem. Soc.*, 1961, **83**, 3720–3722; (g) G. Stork and R. Breslow, The structure of cedrene, *J. Am. Chem. Soc.*, 1953, **75**, 3291; (h) P. Walter, Ueber das feste und flüssige Cedernöl, *Ann. Chem.*, 1841, **39**, 247–251.

5 For selected examples of inter- and intramolecular cycloaddition reactions: (a) S. Poplata, A. Bauer, G. Storch and T. Bach, Intramolecular [2+2] photocycloaddition of cyclic enones: selectivity control by Lewis acids and mechanistic implications, *Chem.-Eur. J.*, 2019, **25**, 8135–8148; (b) A. K. Clarke, J. T. Liddon, J. D. Cuthbertson, R. J. Taylor and W. P. Unsworth, Dearomatisation approaches to spirocyclic dienones *via* the electrophilic activation of alkynes, *Org. Biomol. Chem.*, 2017, **15**, 233–245; (c) B. S. Donslund, R. P. Nielsen, S. M. Mønsted and K. A. Jørgensen, Benzofulvenes in trienamine catalysis: stereoselective spiroindene synthesis, *Angew. Chem., Int. Ed.*, 2016, **55**, 11124–11128; (d) K. Yoshida, Y. Itatsu, Y. Fujino, H. Inoue and K. Takao, Enantioselective organocatalytic construction of spiroindane derivatives by intramolecular Friedel–Crafts-type 1,4-addition, *Angew. Chem., Int. Ed.*, 2016, **55**, 6734–6738; (e) J. Zheng, S.-B. Wang, C. Zheng and S.-L. You, Asymmetric dearomatization of naphthols *via* a Rh-catalyzed C(sp²)–H functionalization/annulation reaction, *J. Am. Chem. Soc.*, 2015, **137**, 4880–4883; (f) L. Yang, H. Zheng, L. Luo, J. Nan, J. Liu, Y. Wang and X. Luan, Palladium-catalyzed dynamic kinetic asymmetric transformation of racemic biaryls: axial-to-central chirality transfer, *J. Am. Chem. Soc.*, 2015, **137**, 4876–4879; (g) S. Rousseaux, J. García-Fortanet, M. A. Del Aguil Sanchez and S. L. Buchwald, Palladium(0)-



catalyzed arylative dearomatization of phenols. Au-Containing all-carbon 1,3-dipoles: generation and [3+2] cycloaddition reactions, *J. Am. Chem. Soc.*, 2011, **133**, 9282–9285.

6 (a) X. M. Zhang, Y. Q. Tu, F. M. Zhang, Z. H. Chen and S. H. Wang, Recent applications of the 1,2-carbon atom migration strategy in complex natural product total synthesis, *Chem. Soc. Rev.*, 2017, **46**, 2272–2305; (b) S. H. Hou, Y. Q. Tu, S. H. Wang, C. C. Xi, F. M. Zhang, S. H. Wang, Y. T. Li and L. Liu, Total syntheses of the tetracyclic cyclopiane diterpenes conidiogenone, conidiogenol, and conidiogenone B, *Angew. Chem., Int. Ed.*, 2016, **55**, 4456–4460; (c) S. H. Wang, B. S. Li and Y. Q. Tu, Catalytic asymmetric semipinacol rearrangements, *Chem. Commun.*, 2014, **50**, 2393–2408; (d) S. H. Wang, Y. Q. Tu and M. Tang, in: *Comprehensive Organic Synthesis II*, ed. G. A. Molander and P. Knochel, Pergamon, Oxford, 2014, vol. 3, pp. 795–852; (e) Z. L. Song, C. A. Fan and Y. Q. Tu, Semipinacol rearrangement in natural product synthesis, *Chem. Rev.*, 2011, **111**, 7523–7556; (f) B. Wang and Y. Q. Tu, Stereoselective construction of quaternary carbon stereocenters *via* a semipinacol rearrangement strategy, *Acc. Chem. Res.*, 2011, **44**, 1207–1222; (g) E. Zhang, C. A. Fan, Y. Q. Tu, F. M. Zhang and Y. L. Song, Organocatalytic asymmetric vinylogous α -ketol rearrangement: enantioselective construction of chiral all-carbon quaternary stereocenters in spirocyclic diketones *via* semipinacol-type 1,2-carbon migration, *J. Am. Chem. Soc.*, 2009, **131**, 14626–14627.

7 For selected examples: (a) H. Wu, Q. Wang and J. Zhu, Copper-catalyzed enantioselective domino arylation/semipinacol rearrangement of allylic alcohols with diaryliodonium salts, *Chem.-Eur. J.*, 2017, **23**, 13037–13041; (b) D. H. Lukamto and M. J. Gaunt, Enantioselective copper-catalyzed arylation-driven semipinacol rearrangement of tertiary allylic alcohols with diaryliodonium salts, *J. Am. Chem. Soc.*, 2017, **139**, 9160–9163; (c) W. Li, X. Liu, F. Tan, X. Hao, J. Zheng, L. Lin and X. Feng, Catalytic asymmetric homologation of α -ketosteres with α -diazoesters: synthesis of succinate derivatives with chiral quaternary centers, *Angew. Chem., Int. Ed.*, 2013, **52**, 10883–10886; (d) F. Romanov-Michailidis, L. Guenée and A. Alexakis, Enantioselective organocatalytic fluorination-induced Wagner-Meerwein rearrangement, *Angew. Chem., Int. Ed.*, 2013, **52**, 9266–9270; (e) W. Li, X. Liu, X. Hao, Y. Cai, L. Lin and X. Feng, A catalytic asymmetric ring-expansion reaction of isatins and α -alkyl- α -diazoesters: highly efficient synthesis of functionalized 2-quinolone derivatives, *Angew. Chem., Int. Ed.*, 2012, **51**, 8644–8647; (f) W. Li, J. Wang, X. Hu, K. Shen, W. Wang, Y. Chu, L. Lin, X. Liu and X. Feng, Catalytic asymmetric Roskamp reaction of α -alkyl- α -diazoesters with aromatic aldehydes: highly enantioselective synthesis of α -alkyl- β -keto esters, *J. Am. Chem. Soc.*, 2010, **132**, 8532–8533; (g) H. S. Yeom, Y. Lee, J. Jeong, E. So, S. Hwang, J. E. Lee, S. S. Lee and S. Shin, Stereoselective one-pot synthesis of 1-aminoindanes and 5,6-fused azacycles using a gold-catalyzed redox-pinacol-

Mannich–Michael cascade, *Angew. Chem., Int. Ed.*, 2010, **49**, 1611–1614; (h) I. R. Pottie, S. N. Crane, A. L. Gosse, D. O. Miller and D. J. Burnell, Geminal acylation of α -heterosubstituted cyclohexanones and their ketals, *Can. J. Chem.*, 2010, **88**, 1118–1124; (i) X. Huang and L. Zhang, Two-step formal [3+2] cycloaddition of enones/enals and allenyl MOM ether: Gold-catalyzed highly diastereoselective synthesis of cyclopentanone enol ether containing an all-carbon quaternary center, *J. Am. Chem. Soc.*, 2007, **129**, 6398–6399; (j) S. F. Kirsch, J. T. Binder, B. Crone, A. Duschek, T. T. Haug, C. Liebert and H. Menz, Catalyzed tandem reaction of 3-silyloxy-1,5-enynes consisting of cyclization and pinacol rearrangement, *Angew. Chem., Int. Ed.*, 2007, **46**, 2310–2313; (k) G. R. Daké, M. D. B. Fenster, M. Fleury and B. O. Patrick, Investigations of α -siloxy-epoxide ring expansions forming 1-azaspirocyclic ketones, *J. Org. Chem.*, 2004, **69**, 5676–5683.

8 For selected examples of the Au-catalyzed 1,3-OAc shift of propargylic ester and cyclization: (a) M. Brandstätter, N. Huwylera and E. M. Carreira, Gold(I)-catalyzed stereoselective cyclization of 1,3-enyne aldehydes by a 1,3-acyloxy migration/Nazarov cyclization/aldol addition cascade, *Chem. Sci.*, 2019, **10**, 8219–8223; (b) S. K. Thummanapelli, S. Hosseyni, Y. Su, N. G. Akhmedov and X. Shi, Ligand-controlled gold-catalyzed cycloisomerization of 1,*n*-enye esters toward synthesis of dihydronaphthalene, *Chem. Commun.*, 2016, **52**, 7687–7690; (c) C. Chen, Y. Zou, X. Chen, X. Zhang, W. Rao and P. W. H. Chan, Gold-catalyzed tandem 1,3-migration/double cyclopropanation of 1-ene-4,*n*-diyne esters to tetracyclodecene and tetracycloundecene derivatives, *Org. Lett.*, 2016, **18**, 4730–4733; (d) Z. Cao and F. Gagosz, Gold-catalyzed tandem cycloisomerization/Cope rearrangement: an efficient access to the hydroazulenic motif, *Angew. Chem., Int. Ed.*, 2013, **52**, 9014–9018; (e) Y. Chen, M. Chen and Y. Liu, Gold-catalyzed cascade cyclizations of 1,6-diynyl carbonates to benzo[*b*]fluorenes involving arylation of oxocarbenium ion intermediates and decarboxylative etherification, *Angew. Chem., Int. Ed.*, 2012, **51**, 6493–6497; (f) D. Lebœuf, A. Simonneau, C. Aubert, M. Malacria, V. Gandon and L. Fensterbank, Gold-catalyzed 1,3-acyloxy migration/5-exo-dig cyclization/1,5-acyl migration of diynyl esters, *Angew. Chem., Int. Ed.*, 2011, **50**, 6868–6871; (g) S. Bhunia and R.-S. Liu, Gold-catalyzed 1,3-addition of a sp^3 -hybridized C–H bond to alkenylcarbenoid intermediate, *J. Am. Chem. Soc.*, 2008, **130**, 16488–16489; (h) F.-Q. Shi, X. Li, Y. Xia, L. Zhang and Z.-X. Yu, DFT study of the mechanisms of in water Au(I)-catalyzed tandem [3,3]-rearrangement/Nazarov reaction/[1,2]-hydrogen shift of enynyl acetates: a proton-transport catalysis strategy in the water-catalyzed [1,2]-hydrogen shift, *J. Am. Chem. Soc.*, 2007, **129**, 15503–15512; (i) A. Buzas and F. Gagosz, Gold(I) catalyzed isomerization of 5-en-2-yn-1-yl acetates: an efficient access to acetoxy bicyclo[3.1.0]hexenes and 2-cycloalken-1-ones, *J. Am. Chem. Soc.*, 2006, **128**, 12614–12615; (j) J. Zhao, C. O. Hughes and F. D. Toste, Synthesis of aromatic ketones by a transition metal-catalyzed tandem



sequence, *J. Am. Chem. Soc.*, 2006, **128**, 7436–7437; (k) L. Zhang and S. Wang, Efficient synthesis of cyclopentenones from enynyl acetates *via* tandem Au(I)-catalyzed 3,3-rearrangement and the Nazarov reaction, *J. Am. Chem. Soc.*, 2006, **128**, 1442–1443.

9 For selected reviews: (a) D. Pflasterer and A. S. Hashmi, Gold catalysis in total synthesis – recent achievements, *Chem. Soc. Rev.*, 2016, **45**, 1331–1367; (b) Y. Zhu, L. Sun, P. Lu and Y. Wang, Recent advances on the Lewis acid-catalyzed cascade rearrangements of propargylic alcohols and their derivatives, *ACS Catal.*, 2014, **4**, 1911–1925; (c) R. Kazem Shiroodi and V. Gevorgyan, Metal-catalyzed double migratory cascade reactions of propargylic esters and phosphates, *Chem. Soc. Rev.*, 2013, **42**, 4991–5001; (d) N. Krause and C. Winter, Gold-catalyzed nucleophilic cyclization of functionalized allenes: a powerful access to carbo- and heterocycles, *Chem. Rev.*, 2011, **111**, 1994–2009.

10 (a) J. D. White, R. G. Carter, K. F. Sundermann and M. Wartmann, Total synthesis of epothilone B, epothilone D, and *cis*- and *trans*-9,10-dehydroepothilone D, *J. Am. Chem. Soc.*, 2001, **123**, 5407–5413; (b) R. D. Stephens and C. E. Castro, The substitution of aryl iodides with cuprous acetylides. A synthesis of tolanes and heterocyclics, *J. Org. Chem.*, 1963, **28**, 3313–3315.

11 (a) A. W. Sromek, A. V. Kel'in and V. Gevorgyan, A novel 1,2-migration of acyloxy, phosphatyloxy, and sulfonyloxy groups in allenes: efficient synthesis of tri- and tetrasubstituted furans, *Angew. Chem., Int. Ed.*, 2004, **43**, 2280–2282; (b) T. Schwier, A. W. Sromek, D. M. L. Yap, D. Chernyak and V. Gevorgyan, Mechanistically diverse copper-, silver-, and gold-catalyzed acyloxy and phosphatyloxy migrations: efficient synthesis of heterocycles *via* cascade migration/cycloisomerization approach, *J. Am. Chem. Soc.*, 2007, **129**, 9868–9878.

12 For detailed optimization of tandem reaction conditions, see ESI.†

13 M. Jia and M. Bandini, Counterion effects in homogeneous gold catalysis, *ACS Catal.*, 2015, **5**, 1638–1652.

14 For the X-ray crystallography of corresponding derivatives, please see ESI.†

15 (a) J. D. Medina and L. D. Genova, Alkaloids of the bark of *Aspidosperma rhombeosignatum*, *Planta Med.*, 1979, **37**, 165–167; (b) R. B. Woodward and W. J. Brehm, The structure of strychnine. Formulation of the neo bases, *J. Am. Chem. Soc.*, 1948, **70**, 2107–2115.

16 (a) S. Li, P. Zhang, Y. Li, S. Lu, J. Gong and Z. Yang, Diastereoselective synthesis of diquinanes and triquinanes bearing vicinal quaternary carbon stereocenters from acyclic allene-based precursors *via* a cascade reaction, *Org. Lett.*, 2017, **19**, 4416–4419; (b) E. V. Prusov, Construction of quaternary stereogenic centers in the total synthesis of natural products, *Angew. Chem., Int. Ed.*, 2017, **56**, 14356–14358; (c) J.-K. Eggden and H. W. Moore, A new tandem route to angular tetraquinanes. Synthesis of the waihoensene ring system, *Org. Lett.*, 1999, **1**, 375–377.

17 H. Lee, T. Kang and H. Y. Lee, Total synthesis of (\pm)-waihoensene, *Angew. Chem., Int. Ed.*, 2017, **56**, 8254–8257.

18 For detailed optimization of reaction conditions, see ESI.†

