Spiro Compounds

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Facile Stereoselective Approach to Diverse Spiroheterocyclic Tetrahydropyrans: Concise Synthesis of (+)-Broussonetine G and H

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Abstract: *A highly diastereoselective copper-catalyzed multicomponent cyclization of exocyclic enol ethers/enamines with methylene malonate and aldehydes has been developed to furnish spiroheterocyclic tetrahydropyrans in high yields with greater than 95:5 d.r. This method is practical, in that 36 examples, including a range of aldehydes and exo-vinyl heterocycles, are presented. By applying the newly developed method, the total synthesis of (+)-broussonetine G and formal synthesis of (+)-broussonetine H were achieved in a concise way.*

Spiroheterocyclic tetrahydropyran motifs exist widely in natural products.[1,2] These compounds with diverse structures are endowed with various biological activities.[3] For example, (+)-broussonetine G and H, containing [6,5] and [6,6] spiroketal fragments, respectively, are potent glycosidase inhibitors,[3a] virgatolide C with a [6,6]-spiroketal core showed cytotoxicity against HeLa cells,[3b] and penicitrinine A bearing N,O-spiroketal structure was found anti-proliferative activity on multiple tumor types (Figure 1).[3c] For a long time, the synthesis of such compounds has been mainly focused on the intramolecular cyclization strategy,[4,5] and depends on designing elaborate substrates that usually require long linear routes to prepare. Thus, developing general methods for the rapid construction of these motifs from simple starting materials are in high demand.

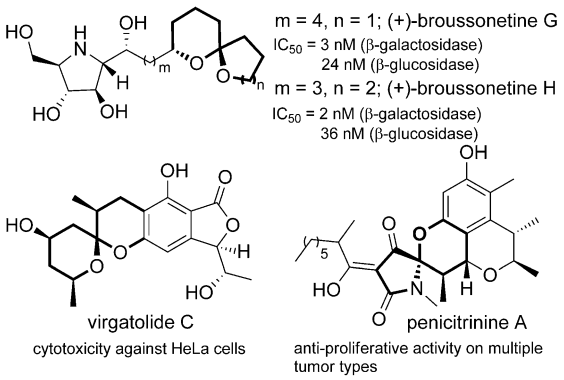
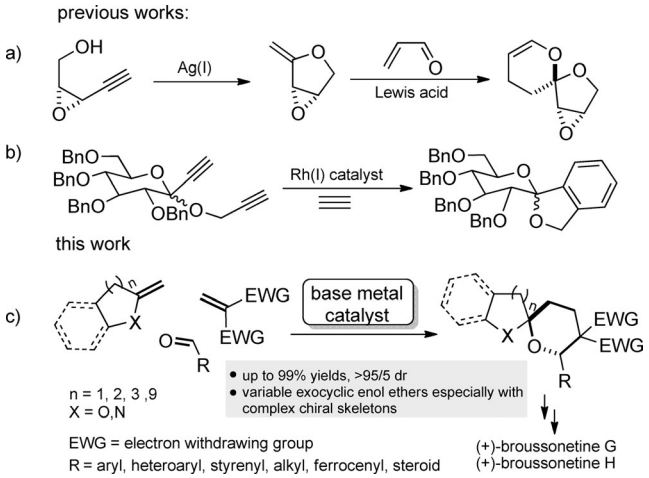


Figure 1. Bioactive molecules with spiroheterocyclic tetrahydropyran motifs.

Intermolecular reactions facilitate the construction of diverse spiroketals from simple starting materials with a view to step economy. In fact, as early as 1988, Pale and co-workers pioneered a two-step synthesis strategy involving a silver ion catalyzed intramolecular cyclization of ω-acetylenic alcohols followed by a Lewis acid catalyzed hetero-Diels–Alder (HDA) reaction to access unsaturated spiroketals (Scheme 1 a).[6,7] In recent years, and using a similar strategy,[8,9]



Scheme 1. Intermolecular approaches to build spiroheterocyclic tetrahydropyrans.

remarkable progress has been made by the groups of Barluenga[8a] and Xu[8b] respectively, in terms of employing noble metals, such as Pd and Au, with different Lewis acids as catalysts to achieve [6,5]-spiroketalizations between alkynols and salicylaldehyde derivatives or oxa-dienophiles. McDonald and co-workers developed a rhodium-catalyzed alkyne cyclotrimerization strategy to synthesize the spiroglycoside from bisalkynylcarbohydrate derivatives (Scheme 1 b).[10] The above-mentioned methods provide effective protocols for the construction of [6,5]-spiroketals.[11] In contrast, for [6,6]-spiroketals, which are also core structures of a series of biologically active natural products, the reported intermolecular examples are still challenging. For example, Feng and co-workers developed an elegant gold(I)/nickel(II) relay catalysis for the synthesis of spiroketals with alkynyl alcohols and keto esters.[9b] They found that by employing hex-5-yn-1-ol

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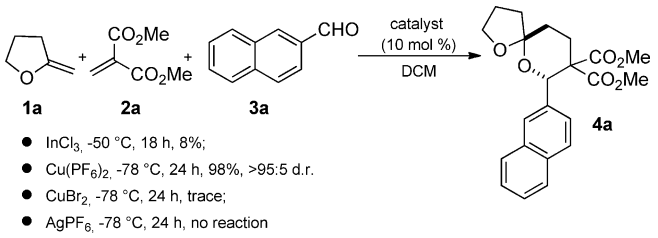
instead of pent-4-yn-1-ol, the yield of the corresponding [6,6]-spiroketal was dramatically decreased from 94 to 50% compared with the [6,5]-spiroketal product, probably because of the fact that the cyclization step with intramolecular alkynols is becomes more difficult with the longer carbon chain. Thus, facile approaches to various spiroheterocyclic tetrahydropyrans, especially those containing larger rings or complicated structures, are still very limited. In this study, we conceived a new tandem cyclization protocol for a base metal catalyzed stereoselective spiroketalization (Scheme 1c).

A diverse range of spiroheterocyclic tetrahydropyrans can be constructed with high efficiency and diastereoselectivity from various exocyclic enol ethers/enamines, methylene malonate, and a very wide scope of aldehydes. By applying this method, the total synthesis of (+)-broussonetine G, the formal synthesis of (+)-broussonetine H, as well as the core structure framing of natural product cycloethaliacumarin[12] were completed in a concise way. Herein, we report the preliminary results.

In recent years, we have developed a series of cyclization reactions by employing methylene malonate (**2a**) as a synthetic building block.[13] In this study, the exocyclic enol ether **1a**, methylene malonate (**2a**), and 2-naphthaldehyde (**3a**) were initially reacted with 10 mol% of $InCl_3$ as a catalyst in dichloromethane (DCM) at −50°C, leading to the desired spiroketal **4a** in only 8% yield (Scheme 2). Further screening

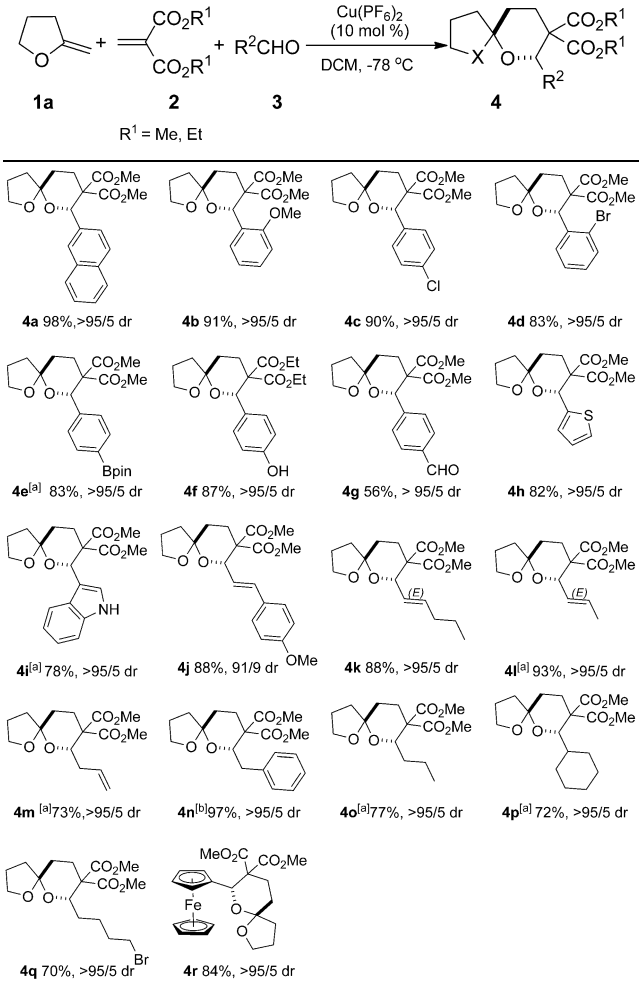


Scheme 2. Tandem reaction of exocyclic enol ether (**1a**), methylene malonate (**2a**), and 2-naphthaldehyde (**3a**) with different Lewis acids.

on the reaction conditions was carried out[14] and $Cu(PF_6)_2$, generated in situ from $CuBr_2$ and $AgPF_6$, was found to be the best catalyst, giving **4a** in 98% yield with > 95:5 d.r. at −78°C after 24 hours. It is worth mentioning that both $CuBr_2$ and $AgPF_6$ could not promote the current reaction at −78°C. The relative configuration of **4a** was confirmed by X-ray crystallography.[15]

Under the optimized reaction conditions, the substrate scope of the reaction was investigated as summarized in Table 1. A range of aldehydes serves as suitable substrates, even those with sensitive functional groups. Aromatic aldehydes bearing substituents at different positions of the phenyl groups, such as 2-MeO, 4-Cl, and 2-Br groups, led to the spiroketals **4b–d** in 83–91% yields with greater than 95:5 d.r. Aromatic aldehydes containing easily transformed functional groups, such as 4-bpin, 4-hydoxy, and formyl groups, were tolerated, providing **4e–g** in up to 87% yield with greater than 95:5 d.r. In addition, 2-formylthiophene and 3-formylindole were also suitable reaction candidates, giving **4h** and **4k**, respectively, in high yields with greater than 95:5 d.r. This

Table 1: Substrate scope with respect to aldehydes.

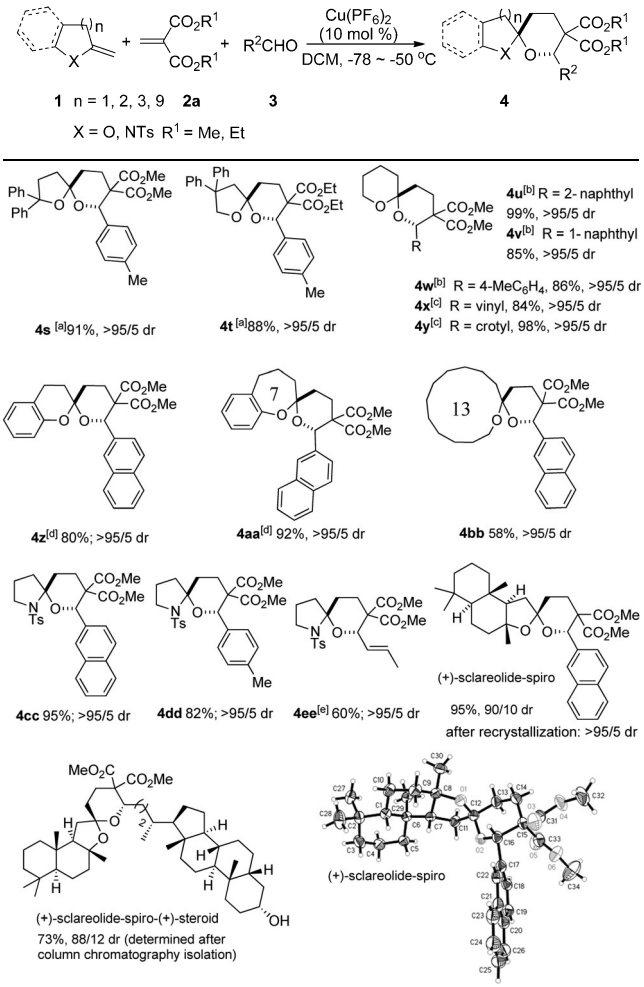


Reaction conditions: **1** (0.6 mmol), **2** (0.6 mmol), **3** (0.2 mmol), $CuBr_2$ (0.02 mmol), and $AgPF_6$ (0.05 mmol) in DCM (2 mL). Yield is that of isolated product. The d.r. value was determined by ^1H NMR analysis of the crude reaction mixture. [a] −78 °C to −50 °C. [b] −78 °C to −50 °C to RT. Bpin = pinacolboryl.

method could also deliver spiroketals with olefin moieties. For examples, when 4-methoxycinnamaldehyd, 2-hexenal, and crotonaldehyde were employed as substrates, **4j–l** were obtained in 88–93% yields with excellent diastereoselectivities. With 3-butenal as substrate, **4m** was afforded in 73% yield with greater than 95:5 d.r. Remarkably, aliphatic aldehydes were totally compatible with the current reaction system. Various aliphatic aldehydes, including 2-phenylacetaldehyde, butyraldehyde, cyclohexanaldehyde, and 5-bromopentanal were employed, and high yields with greater than 95:5 d.r. were achieved to give **4n–q**. Furthermore, **4r,** bearing a ferrocene moiety, could also be prepared by using this method in 84% yield with greater than 95:5 d.r.

Further study showed that this method was compatible with various exocyclic enol ethers. As shown in Table 2, the enol ethers, bearing two phenyl groups on the five-membered ring, could give **4s** and **4t** in 88–91% yields with greater than 95:5 d.r. Compared with those previously reported strategies involving noble metal catalyzed intramolecular cyclization of

Table 2: Substrate scope with respect to **1**.

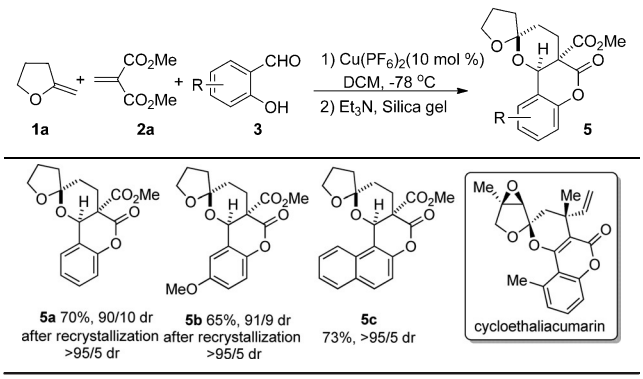


Reaction conditions: **1** (0.6 mmol), **2** (0.6 mmol), **3** (0.2 mmol), $CuBr_2$ (0.02 mmol), and $AgPF_6$ (0.05 mmol) in DCM (2 mL). Yield is that of isolated products. The d.r. value was determined by ^1H NMR analysis of the crude reaction mixture. [a] −78 °C. [b] −78 °C to RT. [c] −78 °C to −50 °C to RT. [d] Purified by recrystallization. [e] $Cu(OTf)_2$ was used as catalyst. Tf = trifluoromethanesulfonyl, Ts = tosyl.

alkynols, the current method broke the limitation of the five-membered ring enol ether substrates. Six-membered exocyclic enol ethers were very good substrates, and could react with a broad range of aldehydes smoothly, including both aromatic and aliphatic aldehydes (**4u–z**, 80–99% yields, > 95:5 d.r.). It was found that the excellent diastereoselectivity was controlled by a thermodynamic process.[14] Seven-membered exocyclic enol ethers, and even 13-membered enol ethers, were also suitable substrates, leading to the **4aa** and **4bb** in 92 and 58% yields, respectively, with excellent diastereoselectivities. Furthermore, these good results were observed not only for enol ethers, but also for exocyclic enamines, and the corresponding products **4cc–ee** were obtained in good to high yields with excellent d.r. values for both aromatic and aliphatic aldehydes. Remarkably, to test the practicability of this reaction on transforming complex molecules during late-stage organic synthesis, asymmetric reactions on (*R*)-(+)-sclareolide were carried out. With 2-naphthaldehyde, the resulting optically active product (+)-sclareolide-spiro was obtained in 95% yield with 90:10 d.r. (> 95:5 d.r., after recrystallization). This reaction was effective in joining two complex moieties through one tetrahydropyranic cycle. With a lithocholic acid derived aldehyde, (*R*)-(+)-sclareolide was linked to a steroid moiety to give the corresponding optically active product (+)-sclareolide-spiro-(+)-steroid in 73% yield with 88:12 d.r. The relative configurations of **4u** and (+)-sclareolide-spiro were confirmed by X-ray crystallography.[15] These examples shown a high degree of remote stereocontrol in a thermodynamic process.

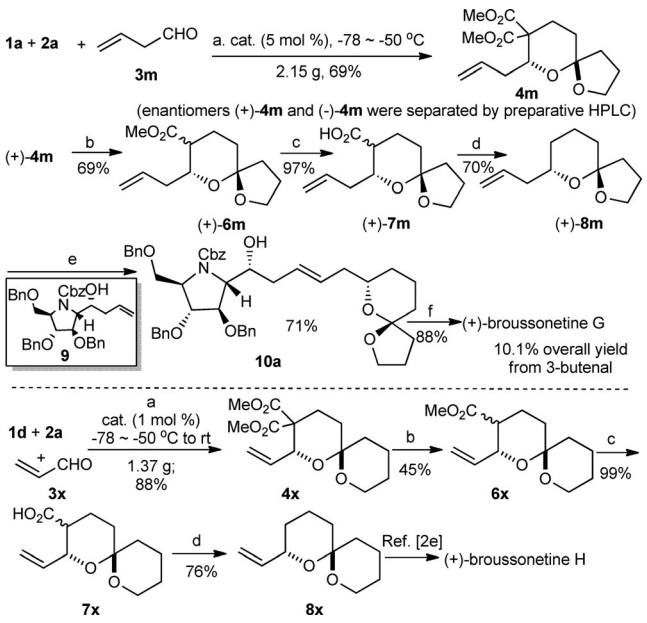
Moreover, when salicylaldehydes were employed as substrates, the spiroketalization followed by an intramolecular transesterification occurred to give the corresponding tetracyclic spiroketals **5a–c** in 65–73% yields with excellent d.r. values (Table 3). It is worth mentioning that a tetracyclic spiroketal is the core structure of the natural product cycloethaliacumarin.[12] The relative configuration of **5c** was confirmed by X-ray crystallography.[15]

Table 3: Construction of tetracyclic spiroketals with salicylaldehydes.



Reaction conditions: **1** (0.6 mmol), **2** (0.6 mmol), **3** (0.2 mmol), $CuBr_2$ (0.02 mmol), and $AgPF_6$ (0.05 mmol) in DCM (2 mL) at −78 °C, then Et3N (0.5 mL) and silica gel was added at −78 °C until **3** disappeared. Yield is that of isolated products. The d.r. value was determined by ^1H NMR spectroscopy.

Inspired by the synthetic efficiency to form spiroketals with the current method, we tried to apply it to construct the basic skeletons of the biologically active natural products (+)-broussonetine G and H (Scheme 3).[3a] The catalyst loading could be decreased to 1 mol%, and the scale-up tandem cyclization reactions with both five- and six- membered ring enol ethers were applied as the key step to access **4m** and **4x** with excellent diastereoselectivities. The two enantiomers (+)-**4m** and (−)-**4m** could be easily separated by preparative high-performance liquid chromatography (HPLC).[14] (+)-**4m** was then treated with LiCl to give mono-decarboxylated product (+)-**6m**, followed by a hydrolysis reaction, affording (+)-**7m** in 97% yield. The carboxy group was removed through a Barton ester free-radical reaction, and the resulting (+)-**8m** was then connected with an arabinofuranose-derived synthetic intermediate **9**[16] by employing the Hoveyda–Grubbs(II) catalyst to give **10a**. The total synthesis of (+)-broussonetine G was completed by the final hydrogena-



Scheme 3. Gram-scale synthesis, total synthesis of (+)-broussonetine G, and formal synthesis of (+)-broussonetine H. Reagents and conditions: a) $Cu(PF_6)_2$, DCM; b) LiCl, H_2O, dimethyl sulfoxide (DMSO), 130 °C; c) LiOH·H_2O, MeOH/H_2O, 50 °C; d) dipyrithione, *n*-Bu_3P, *n*-Bu_3SnH, dark, benzene at RT for 3 h, then azodiisobutyronitrile (AIBN) at 80 °C; e) Hoveyda–Grubbs(II), DCM, 55 °C; f) Pd/C, H_2, MeOH, HCl (aq), RT.

tion of **10a** in a linear sequence of six steps from 3-butenal with 10.1% overall yield. Meanwhile, with (−)-**4m**, the diastereomer of (+)-broussonetine G was also prepared in the same way,[14] and provided a useful method in view of the demand for structural diversity for the study of structure–activity relationships (SARs). Similarly, **4x** was converted into **8x,** which could be transformed into (+)-broussonetine H in two steps by a known procedure.[2e]

In summary, the first stereoselective multicomponent tandem cyclizations of exocyclic enol ethers/enamines, methylene malonate, and aldehydes were developed. They were catalyzed by a copper(II) system to furnish the spiroheterocyclic tetrahydropyrans in up to 99% yields with > 95:5 d.r. The reaction has a broad substrate scope as evidenced. A wide range of aldehydes, as well as different *exo*-vinyl heterocycles all work well. This newly developed method was competent in late-stage modifications of complex molecules, and was applied to the total synthesis of (+)-broussonetine G and formal synthesis of (+)-broussonetine H. The spiroketal was transformed into (+)-broussonetine G in a linear sequence of six steps from 3-butenal with 10.1% overall yield. Further studies into additional applications of this reaction are underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: copper · cyclization · diastereoselectivity · natural products · spiro compounds

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