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Gold Catalysis-Facilitated Rapid Synthesis of the Daphnane/Tiglane Tricyclic Core

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Abstract

A concise approach to synthesize the 5-7-6 tricyclic carbon skeleton of the daphnane/tiglane diterpene natural products has been accomplished *via* a sequential gold-catalyzed furan formation and furan-allene [4+3] cycloaddition. This work provides new avenues for rapid and diverted synthesis of the medicinally important daphnane/tiglane diterpenes and their unnatural analogues.

Graphical Abstract

Keywords

Daphnane/Tiglane; Diterpene; Gold catalysis; Furan formation; [4+3] cycloaddition

1. Introduction

The daphnanes and tiglanes, isolated from *thymelaeaceae* and *euphorbiaceae*, are two large groups of structurally diverse diterpene natural products which share a characteristic 5-7-6 tricyclic carbon skeleton.^[1] These structurally complex molecules have received a significant amount of attention due to their appealing chemical structures and promising therapeutic potential. They have demonstrated a broad range of biological activities, including anticancer, antiviral, analgesic, and neurotrophic effects.^[1b,2] For example, kirkine^[3] (**1**, Figure 1), isolated from the roots of *synaptolepis kirkii*, is the most potent

Supplementary Material

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neurotrophically active natural product reported so far. It effectively promotes neuronal survival against serum deprivation in nanomolar concentrations, which is comparable to the nerve growth factor itself. Phorbol (**2**)^[4] is a well-known tumor promotor and protein kinase C activator. On the other hand, phorbol 12-myristate-13 acetate, also a protein kinase C activator, has been advanced into human clinical trials for the treatment of acute myeloid leukaemia. Prostratin (**3**)^[5], is a promising therapeutic agent that targets latent HIV reservoirs. Resiniferatoxin (**4**)^[6] exhibits an analgesic effect through activation of transient receptor potential vanilloid 1 (TRPV1), which induces desensitization of nociceptive neurons.

The structural complexity and promising therapeutic applications of these daphnane and tiglane diterpenes have identified themselves as attractive synthetic targets. Many synthetic approaches toward the core structures of these natural products have been reported since the early 1980s.^[7] These synthetic efforts culminated in the total syntheses of phorbol and resiniferatoxin by Wender^[8] and co-workers, a formal synthesis of phorbol by Cha^[9] et al., a total synthesis of crotophorbolone, a derivative of the daphnane/tiglane diterpenes, by the Inoue^[10] group, and an impressive 19-step total synthesis of phorbol by the Baran group^[11] (Figure 2). The Wender synthesis features a [5+2] cycloaddition to construct the 6,7-fused bicycle. The Cha synthesis utilized a [4+3] cycloaddition to build the central 7-membered ring and the Inoue group used a radical cyclization to close the 7-membered ring. An allene-alkene Pauson-Khand reaction^[12] was employed by the Baran group to set up the 5,7-fused ring system.

Despite all these synthetic efforts, concise and highly efficient synthetic routes toward these complex diterpenes are still valuable and necessary. Herein, we report our efforts in developing a synthetic approach to rapidly construct the 5-7-6 carbocyclic ring system by using a gold-catalyzed furan formation and furan/allene [4+3] cycloaddition.

Gold catalysis has started to play an important role in facilitating total syntheses of complex bioactive natural products.^[13] The gold-catalyzed furan/allene [4+3] cycloaddition, developed by the groups of Mascareñas^[14] and Toste^[15], is a very efficient synthetic method for highly functionalized 7-membered ring construction. Despite the high efficiency in constructing polycyclic ring systems, its application in complex natural product synthesis has been very rare.^[16] Meanwhile, a number of gold-catalyzed furan formation reactions^[17] were reported to access highly substituted furan moieties. Inspired by these works, we envisioned a gold-catalyzed tandem furan formation followed by furan/allene [4+3] cycloaddition as an efficient approach for the synthesis of the daphnane/tiglane 5-7-6 core skeleton (Figure 3, **6**→**10**). This tandem process would start from relatively simple enyne alcohol **6**, which could be readily assembled by a Sonogashira cross coupling. The gold catalyst would selectively activate the alkyne to trigger a 5-*exo-dig* cyclization of the hydroxyl group on the alkyne and generate hydrofuran **7**, which would then isomerize to furan **8**. The gold catalyst would then activate the allene to generate an allylic cation-gold complex for the [4+3] cycloaddition to provide product **10**, which could then be advanced to the daphnane/tiglane diterpenes. This tandem process faces several challenges: (i) How to preferentially activate the alkyne in presence of the allene? (ii) How to avoid other competing cycloisomerization reactions before the furan formation and [4+3] cycloaddition?

(iii) Will the reaction provide the desired stereochemistry? Despite these potential problems, such a tandem process would significantly improve synthetic efficiency by converting relatively simple and readily available starting material such as **6** to complex polycyclic intermediate such as **10**, which resembles the core skeleton of the daphnane/tiglane diterpene natural products.

2. Result and discussion

We designed substrates **6a–6c** with varying substituents on the allene moiety as our model substrates. Their syntheses are summarized in Scheme 1. Fragment **13** is a known compound^[18] which can be synthesized on gram scale in 66% yield through a Vilsmeier-Haack reaction of cyclopentanone **11** followed by a sodium borohydride reduction of the resulting aldehyde **12**. Allenes **17a–17c** were synthesized utilizing the Ma's protocol for allene synthesis^[19] followed by propargylation. Sonogashira cross coupling united **13** and **17** successfully and gave the desired coupling products from 52% to 86% yield. In these Sonogashira couplings, the freeze-pump-thaw^[20] technique is crucial for high yields; otherwise, a significant amount of alkyne dimerization leads to a dramatic drop of the reaction yield.

We next investigated the feasibility of the gold-catalyzed tandem cyclization and cycloaddition process under various reaction conditions on substrate **6a** (Table 1). Initially, the commonly used gold catalyst systems reported for the [4+3] cycloadditions were tested. To our disappointment, conditions such as $\text{PPh}_3\text{AuNTf}_2$ (entries 1 and 4), $\text{tBuXPhosAuCl/AgSbF}_6$ (entry 2), and IPrAuCl/AgSbF_6 (entry 3) only gave very complex mixtures, indicating that these highly reactive catalyst systems may be promoting unwanted cycloisomerization pathways instead of the first furan formation step. The combination of $\text{PPh}_3\text{AuCl/AgOTf}$ in THF was able to produce furan product **8a** in good yield (65% to 72%), but it failed to promote the second [4+3] cycloaddition step (entry 6). Interestingly, the furan formation reaction became unproductive by simply changing solvent from THF to DCE (entry 5) or adding molecular sieves (entry 7) or NaHCO_3 (entry 8).

After unfruitful efforts in realizing a tandem gold-catalyzed furan formation and furan-allene [4+3] cycloaddition by using one gold catalyst system, we decided to run the [4+3] cycloaddition separately and a number of catalysts, silver salts and solvents were evaluated (Table 2). The IPrAuCl/AgSbF_6 combination was effective to catalyze the [4+3] cycloaddition and the cycloaddition product was obtained as a 1.4:1 (**10a:10a'**) mixture of isomers in 35% total yield. Molecular sieves were found to be beneficial for the cycloaddition (entry 2), while coordinating solvents such as CH_3CN (entry 3) and THF (entry 4 and 8) inhibited the reaction process. PtCl_2/CO was also ineffective (entry 5). While $\text{DPPM}(\text{AuCl})_2/\text{AgSbF}_6$ gave no product at room temperature, the combination of $\text{tBuXPhosAuCl/AgSbF}_6$ in DCE at 60 °C gave the best yield so far and products **10a** and **10a'** were obtained in 74% yield, again as 1.4:1 mixture. Overall, electron-rich and bulky ligand-gold catalyst systems are critical for this transformation. Efforts to realize a one-pot furan formation and furan-allene [4+3] cycloaddition of **8a** by using two different gold catalyst systems have not been successful so far.

Since the ratio for desired product (**10a**) and the double bond isomerized product (**10a'**) is unsatisfactory and can not be tuned by changing the catalyst system, we then investigated the substituent effect on the allene moiety and wondered how different substituent groups might affect this selectivity. Substrates **6b** (R = H) and **6c** (R = CH₂OBn) were evaluated (Scheme 2). Both **6b** and **6c** underwent the furan formation reaction smoothly and products **8b** and **8c** were produced in 68% and 63% yields, respectively. While **8b** turned out to be a poor substrate for the gold-catalyzed [4+3] cycloaddition reaction, **8c** did give cycloaddition products in 60% and a slight ratio increase of the desired product **10c** and the double bond isomerized product **10c'** was observed under the ^tBuXPhosAuCl/AgSbF₆ conditions. This result indicates the possibility of improving the selectivity by tuning the electronic properties of the substituent on the allene part.

3. Conclusion

In conclusion, we have developed a concise synthetic approach to the core carbon skeleton of the daphnane/tiglane diterpenes. The key features of this synthetic route include rapid synthesis of the precursor using a Sonogashira coupling reaction and a sequential gold-catalyzed furan formation and furan/allene [4+3] cycloaddition to assemble the 5-7-6 carbocyclic ring system. This study demonstrates that the gold-catalyzed [4 + 3] cycloaddition of furan/allene can be applied to the construction of a complex oxabridged polycyclic system in a stereoselective manner. Further syntheses of daphnane/tiglane and related diterpene natural products as well as their unnatural analogs using this approach are currently in progress and will be reported in due course.

4. Experimental section

4.1. (2-bromocyclopent-1-en-1-yl)methanol(**13**)

Compound **13** was synthesized by a reported^[18] procedure. To a stirred solution of dimethylformamide (11.6 mL, 150 mmol) in 45 mL dichloromethane, phosphorus tribromide (11.8 mL, 125 mmol) was added dropwise at 0 °C. The suspension was stirred for an additional 1 hour before a solution of cyclopentanone (4.5 mL, 50 mmol) in 20 mL dichloromethane was added slowly. The reaction mixture was allowed to warm to room temperature and stirred overnight before the addition of a saturated aqueous solution of sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give the crude product as a light yellow liquid, which was used for the next step directly.

To a solution of the above crude product in 45 mL methanol, sodium borohydride (1.9 g, 50 mmol) was added portionwise at 0 °C. After 1 hour, saturated ammonium chloride aqueous solution was added to quench the reaction. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexane/ethyl acetate = 6:1) to give the compound **3** (5.95 g, 66%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 4.25 (s, 2H), 2.74 – 2.62 (m, 2H), 2.52 – 2.39 (m, 2H), 2.02 – 1.92 (m, 2H), 1.69 – 1.45 (br, 1H); ¹³C NMR (125 MHz, CDCl₃) 139.7, 118.2, 60.6, 40.4,

32.6, 21.8; IR (neat): ν = 3313, 2951, 2852, 1655, 1443, 1319, 1245, 1091, 1023, 1002, 959, 894, 697 cm^{-1} .

4.2. dimethyl 2-(5-(benzyloxy)penta-2,3-dien-1-yl)malonate (**16c**)

To a solution of dimethyl 2-(prop-2-yn-1-yl)malonate (1.7 g, 10.0 mmol) in 100 mL dioxane, diisopropylamine (3.48 mL, 25 mmol), copper iodide (950 mg, 5 mmol) and 2-(benzyloxy)acetaldehyde (3.75 mL, 25 mmol) were added at room temperature. The reaction mixture was warmed to 100 °C and stirred for 36 hours. After it was cooled down and quenched with saturated solution of ammonium chloride (100 mL), the aqueous layer was extracted with ethyl acetate (3×100 mL), and the combined organic layers were concentrated *in vacuo*. The crude residue was purified twice by flash column chromatography (hexane/ethyl acetate = 15:1; hexane/DCM = 1:1 to DCM/ethyl acetate = 10:1) on silica gel to afford product **16c** (900 mg, 23%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.37 – 7.27 (m, 5H), 5.44 – 5.18 (m, 2H), 4.52 (s, 2H), 4.01 (pt, J = 7.0, 3.5 Hz, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.51 (t, J = 7.5 Hz, 1H), 2.62 (ddd, J = 7.5, 6.5, 3.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 205.1, 169.3, 138.2, 128.5, 128.0, 127.8, 90.5, 88.7, 72.0, 68.2, 52.7, 51.3, 27.8; IR (neat): ν = 2953, 2857, 1755, 1736, 1441, 1346, 1269, 1233, 1154, 1097, 1071, 740, 700 cm^{-1} ; HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{21}\text{O}_5$ $[\text{M}+\text{H}]^+$ 305.1384, found 305.1390 m/z .

4.3. dimethyl 2-(5-(benzyloxy)penta-2,3-dien-1-yl)-2-(prop-2-yn-1-yl)malonate (**17c**)

To a solution of compound **16c** (390 mg, 1.28 mmol) in 10 mL dimethylformamide, sodium hydride (77 mg, 1.92 mmol) was added at 0 °C. The suspension was stirred for 30 mins before propargyl bromide (0.2 mL, 80% solution in toluene, 1.5 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for overnight. After the reaction was quenched with saturated solution of ammonium chloride (10 mL), the aqueous layer was extracted with ethyl acetate (3 × 30 mL), and the combined organic layers were concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexane/ethyl acetate = 15:1) on silica gel to afford product **17c** (300 mg, 70%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.38 – 7.27 (m, 5H), 5.39 – 5.23 (m, 1H), 5.10 – 5.03 (m, 1H), 4.52 (d, J = 1.0 Hz, 2H), 4.04 (dt, J = 6.9, 1.6 Hz, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 2.87 (dd, J = 2.8, 0.9 Hz, 2H), 2.80 (dd, J = 8.0, 2.3 Hz, 2H), 2.02 – 1.96 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 206.8, 170.1, 138.2, 128.5, 128.0, 127.8, 88.9, 85.7, 78.7, 72.0, 71.7, 68.3, 57.2, 53.0, 32.1, 22.8; IR (neat): ν = 3288, 2953, 1736, 1438, 1293, 1209, 1074, 940, 699 cm^{-1} ; HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{23}\text{O}_5$ $[\text{M}+\text{H}]^+$ 343.1540, found 343.1546 m/z .

4.4. dimethyl 2-(5-(benzyloxy)penta-2,3-dien-1-yl)-2-(3-(2-(hydroxymethyl)cyclopent-1-en-1-yl)prop-2-yn-1-yl)malonate (**6c**)

A mixture of compound **13** (140 mg, 0.8 mmol), compound **17c** (300 mg, 0.88 mmol), $(\text{PPh}_3)_2\text{PdCl}_2$ (28 mg, 0.04 mmol), copper iodide (15 mg, 0.08 mmol) and diisopropylamine (8 mL) was degassed via five freeze-pump-thaw cycles before it was warmed to 70 °C and stirred overnight. After the reaction was quenched with saturated solution of ammonium chloride, the aqueous layer was extracted with ethyl acetate and the combined organic layers were concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexane/ethyl acetate = 5:1 to 2:1) on silica gel to afford product **6c** (180

mg, 52%) as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.41 – 7.27 (m, 5H), 5.41 – 5.25 (m, 1H), 5.12 – 4.96 (m, 1H), 4.51 (s, 2H), 4.40 – 4.17 (m, 2H), 4.02 (dt, J = 7.1, 2.4 Hz, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.02 (s, 2H), 2.81 (dd, J = 8.0, 2.2 Hz, 2H), 2.43 (ddd, J = 9.9, 5.5, 2.1 Hz, 4H), 1.91 – 1.80 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 206.9, 170.3, 149.7, 138.1, 128.5, 128.0, 127.8, 119.8, 89.0, 88.8, 85.8, 79.7, 72.1, 68.4, 60.7, 57.4, 53.0, 37.2, 34.0, 32.4, 24.1, 22.4; IR (neat): ν = 3441, 2957, 2922, 2849, 1737, 1439, 1291, 1210, 1079, 996, 740, 698 cm^{-1} ; HRMS (ESI): calcd for $\text{C}_{26}\text{H}_{31}\text{O}_6$ $[\text{M}+\text{H}]^+$ 439.2115, found 439.2100 m/z .

4.5. dimethyl 2-(5-(benzyloxy)penta-2,3-dien-1-yl)-2-(2-(5,6-dihydro-4H-cyclopenta[c]furan-1-yl)ethyl)malonate(8c)

To a stirred mixture of chloro(triphenylphosphine)gold(I) (9.5 mg, 0.02 mmol) and silver trifluoromethanesulfonate (5 mg, 0.02 mmol) in THF (0.5 mL), a solution of compound **6c** (84 mg, 0.2 mmol) in 1 mL THF was added at room temperature. The reaction mixture was stirred for 1 hour at room temperature before it was quenched with saturated solution of sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the combined organic layers were concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexane/ethyl acetate = 20:1 to 6:1) on silica gel to afford product **8c** (53 mg, 64%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.36 – 7.27 (m, 5H), 6.90 (d, J = 1.4 Hz, 1H), 5.26 (tdd, J = 6.6, 4.4, 2.2 Hz, 1H), 5.06 (tdt, J = 8.2, 6.2, 2.3 Hz, 1H), 4.49 (s, 2H), 4.02 (ddd, J = 7.0, 2.3, 1.0 Hz, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 2.68 (dd, J = 8.0, 2.3 Hz, 2H), 2.58 – 2.46 (m, 6H), 2.34 – 2.24 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 206.6, 171.3, 143.9, 138.2, 133.5, 130.9, 128.5, 128.0, 127.8, 88.8, 86.1, 72.0, 68.3, 57.4, 52.7, 32.6, 32.4, 30.4, 23.5, 23.4, 22.6; IR (neat): ν = 2950, 2857, 1735, 1449, 1275, 1241, 1204, 1182, 1091, 746, 702 cm^{-1} ; HRMS (ESI): calcd for $\text{C}_{26}\text{H}_{31}\text{O}_6$ $[\text{M}+\text{H}]^+$ 439.2115, found 439.2114 m/z .

4.6. dimethyl (4R,6aR,10aR)-5-((benzyloxy)methyl)-1,2,3,4,6a,7,9,10-octahydro-8H-4,10a-epoxybenzo[e]azulene-8,8-dicarboxylate(10c) and dimethyl (4S,5R,10aR)-5-((benzyloxy)methyl)-1,2,3,4,5,7,9,10-octahydro-8H-4,10a-epoxybenzo[e]azulene-8,8-dicarboxylate (10c')

To a suspension of activated 4 Å molecular sieves (30 mg) in 0.5 mL dichloroethene in 8 mL vial, chloro[2-di-tert-butyl(2',4',6'-triisopropylbiphenyl)phosphine]gold(I) (5 mg, 0.01 mmol) and silver hexafluoroantimonate(V) (2.4 mg, 0.01 mmol) was added. The reaction mixture was stirred for 10 minutes at room temperature before substrate **8c** (34 mg, 0.078 mmol) in 0.5 mL dichloroethene was added. The reaction mixture was then warmed to 60 °C and stirred for 5 hours. After the reaction was quenched with saturated solution of ammonium chloride, the aqueous layer was extracted with ethyl acetate and the combined organic layers were concentrated *in vacuo*. The crude residue was purified by flash column chromatography twice (hexane/ethyl acetate = 10:1; dichloromethane/ethyl acetate = 50:1) on silica gel to afford product **10c** (13 mg, 39%) and **10c'** (7 mg, 21%) as colorless oil. **10c**: ^1H NMR (500 MHz, CDCl_3) δ 7.38 – 7.27 (m, 5H), 5.33 (d, J = 3.9 Hz, 1H), 4.63 (s, 1H), 4.48 (q, J = 11.9 Hz, 2H), 3.92 (d, J = 1.2 Hz, 2H), 3.77 (s, 3H), 3.71 (s, 3H), 2.40 (ddt, J = 14.1, 7.8, 2.5 Hz, 2H), 2.31 – 2.18 (m, 5H), 2.12 – 1.94 (m, 3H), 1.86 (dddd, J = 23.8, 19.0, 11.1, 3.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.3, 171.4, 157.7, 146.4, 140.7, 138.2, 128.5, 127.8, 127.7, 126.5, 80.8, 72.1, 71.4, 55.0, 52.9, 52.7, 33.7, 32.1, 29.4, 29.0,

27.7, 26.3, 26.1; IR (neat): ν = 2951, 2850, 1732, 1454, 1435, 1237, 1176, 1077, 1028, 986, 867, 739, 699 cm^{-1} ; HRMS (ESI): calcd for $\text{C}_{26}\text{H}_{31}\text{O}_6$ $[\text{M}+\text{H}]^+$ 439.2115, found 439.2110 m/z . **10c'**: ^1H NMR (500 MHz, CDCl_3) δ 7.39 – 7.27 (m, 5H), 5.02 (s, 1H), 4.88 (d, J = 5.6 Hz, 1H), 4.52 – 4.42 (m, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.26 (dd, J = 8.7, 6.2 Hz, 1H), 3.20 – 3.12 (m, 1H), 3.11 – 3.05 (m, 1H), 2.95 (dd, J = 15.6, 2.8 Hz, 1H), 2.52 – 2.38 (m, 4H), 2.38 – 2.30 (m, 1H), 2.30 – 2.22 (m, 2H), 2.04 – 1.85 (m, 3H), 1.77 – 1.70 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.3, 170.5, 159.0, 143.8, 140.1, 138.1, 128.5, 127.8, 118.7, 80.7, 77.8, 73.4, 70.1, 54.7, 53.0, 52.8, 38.3, 37.2, 29.6, 29.1, 28.7, 27.7, 27.3; IR (neat): ν = 2952, 2850, 1735, 1451, 1307, 1250, 1163, 1098, 1073, 1014, 992, 895, 744, 700 cm^{-1} ; HRMS (ESI): calcd for $\text{C}_{26}\text{H}_{31}\text{O}_6$ $[\text{M}+\text{H}]^+$ 439.2115, found 439.2108 m/z .

Supplementary Material

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Figure 1.
Representative daphhanane/tigliane diterpenes

Wender: [5+2] Cycloaddition **Cha: [4+3] Cycloaddition** **Inoue: Radical Cyclization** **Baran: Pauson-Khand Reaction**

Figure 2.
Selected strategies for daphanane/tigliane synthesis

Figure 3.
Proposed synthesis of the daphnane/tiglane 5-7-6 tricyclic ring system via tandem gold catalysis

Scheme 1.
Synthesis of model substrates **6a–6c**

Scheme 2. Gold-catalyzed furan formation and [4+3] cycloaddition of **6b** and **6c**.

Table 1

Condition optimization for the tandem process

entry	condition	result
1	10% PPh ₃ AuNTf ₂ , toluene, 60–70 °C	complex mixture
2	10% ^t BuXPhosAuCl/AgSbF ₆ , DCE, –20 °C to RT	decomposed
3	10% IPrAuCl/AgSbF ₆ , DCM, RT.	complex mixture
4	10% PPh ₃ AuNTf ₂ , DCM, 0 °C	8a , 30% brsm (60% con.)
5	10% PPh ₃ AuCl/AgOTf, DCE, RT	complex mixture
6	10% PPh ₃ AuCl/AgOTf, THF, RT	8a , 65% to 72%
7	10% PPh ₃ AuCl/AgOTf, THF, RT, 4 Å MS	no reaction
8	10% PPh ₃ AuCl/AgOTf, THF, RT, NaHCO ₃	very low conversion

Table 2

Condition optimization for the [4+3] cycloaddition

entry	condition	result
1	20% IPrAuCl/AgSbF ₆ , DCM, RT	10a:10a' = 1.4: 1 (35%)
2	20% IPrAuCl/AgSbF ₆ , DCE, RT, 4 Å MS	10a:10a' = 1.4: 1 (50%)
3	20% IPrAuCl/AgSbF ₆ , CH ₃ CN, RT, 4 Å MS	No reaction
4	20% IPrAuCl/AgSbF ₆ , THF, RT, 4 Å MS	trace
5	20% PtCl ₂ /CO, PhMe, reflux	complex mixture
6	10% DPPM(AuCl) ₂ /AgSbF ₆ , DCE, RT, 4 Å MS	No reaction
7	10% ^t BuXPhosAuCl/AgSbF ₆ , DCE, 60 °C 4 Å MS	10a:10a' = 1.4: 1 (74%)
8	10% ^t BuXPhosAuCl/AgSbF ₆ , THF, 60 °C 4 Å MS	no reaction