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# Gold-catalyzed construction of two adjacent quaternary stereocenters *via* sequential C–H functionalization and aldol annulation†

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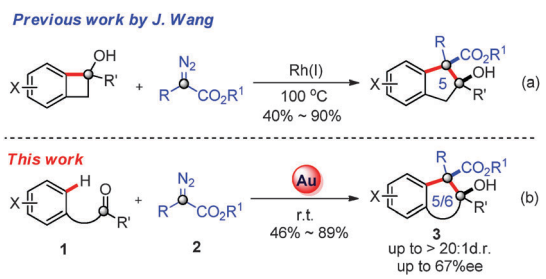
**Herein, a novel and efficient gold-catalyzed intermolecular C($sp^2$)–H functionalization (Friedel–Crafts alkylation) and aldol annulation strategy is presented. This cascade process allows the synthesis of a series of indanol and tetrahydronaphthalenol derivatives with two adjacent quaternary stereocenters. The attractive reaction features are the use of readily available starting materials, good diastereoselectivity, good functional-group tolerance and mild reaction conditions. Furthermore, preliminary results indicate that this transformation is amenable to enantioselectivitive synthesis with further chiral ligand screening and design.**

Quaternary carbon centers are frequently found in a broad range of biologically active molecules, natural products and pharmaceutical agents.[1] Thus, the development of novel methods to efficiently construct quaternary carbon centers,[2] especially all-carbon centers, has received considerable attention recently. Although numerous efforts have been devoted to this field, the efficient construction of these special units still remains a vital challenge due to the steric congestion. Efficient C–C bond formation is believed to be the key issue for the construction of quaternary carbon centers. Over the past decade, metal-catalyzed direct C–H functionalization[3] has emerged as one of the most powerful and encompassing strategies for the formation of C–C bonds. Therefore, the development of a novel methodology to construct all-carbon quaternary centers involving C–H bond functionalization would be highly desirable. Ideally, such an approach requires reaction completion in one convenient operation, mild conditions, functional-group tolerance and the use of readily available starting materials.

However, the carbene transfer reaction of diazo compounds catalyzed by transition-metal complexes, such as rhodium, copper, silver, and palladium represents one of the most effective approaches to not only C–H functionalization[4,5] but also the construction of all-carbon quaternary centers in recent years. Recently, Liang, Yu and Wang demonstrated transition-metal-catalyzed cascade reactions involving diazo compounds to access all-carbon quaternary centers *via* two cross-coupling reactions.[6] However, only one example to construct two adjacent quaternary centers, including one all-carbon stereocenter *via* metal carbene species, has been reported very recently by Wang and his co-workers, who presented a novel rhodium-catalyzed domino reaction to synthesize indanol derivatives between highly-ring-strained benzocyclobutenols and α-diazoesters at 100 °C (Scheme 1a).[7] Given the fact that the indanol and tetrahydronaphthalenol motifs are frequently found in many natural products and biological active compounds,[8] we became interested in developing a novel process for the efficient construction of these key motifs from more readily available precursors. Inspired by ours and Shi's recent study[9] on gold-catalyzed[10] aromatic C–H functionalization with diazoesters,[11] we assumed that these indanols and tetrahydronaphthalenols might rapidly be constructed from much more readily available compounds **1** and diazoesters **2** by the combination of gold-catalyzed aromatic C–H functionalization and an aldol reaction.[12]




Scheme 1 Construction of tetrahydronaphthalenol and indanols with two adjacent stereocenters.

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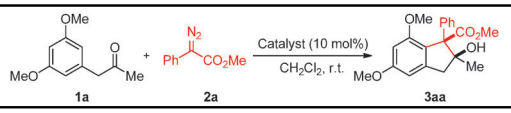
Table 1 Optimization of reaction conditions[a]



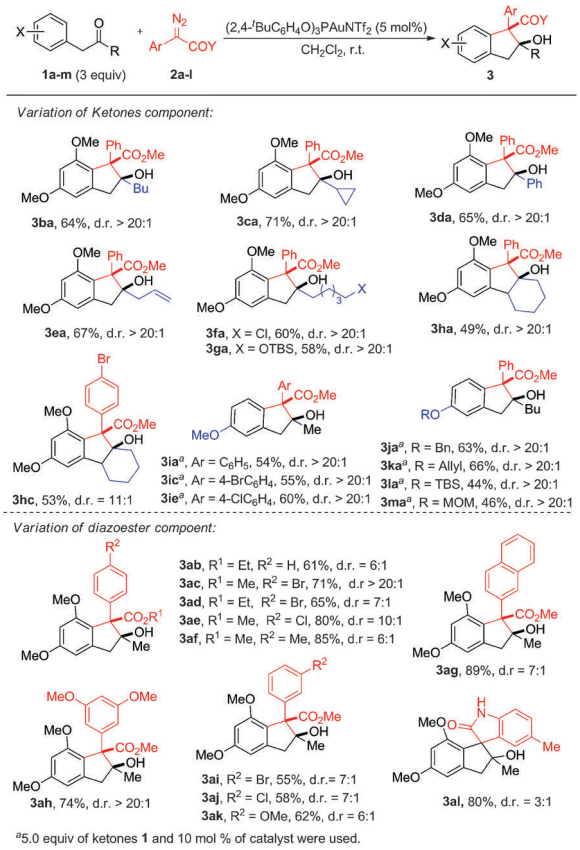

| Entry | Catalyst | Time (min) | Yield[b] (%) | d.r.[c] |
|---|---|---|---|---|
| 1 | $PPh_3AuCl/AgNTf_2$ | 45 | 76 | 9 : 1 |
| 2 | $IPrAuCl/AgNTf_2$ | 45 | 48 | >20 : 1 |
| 3 | $LAuCl/AgNTf_2$ | 45 | 81 | 12 : 1 |
| 4[d] | $LAuCl/AgNTf_2$ | 45 | 68 | 11 : 1 |
| 5[d,e] | $LAuCl/AgNTf_2$ | 45 | 82 (76) | 14: 1 |
| 6 | $AgNTf_2$ | 45 | 38 | 5 : 1 |

[a] The reaction was carried out with **1a** (0.3 mmol), **2a** (0.2 mmol), and catalyst (10 mol%) in solvent (4 mL) at room temperature. [b] Total NMR yield of two isomers. The numbers in parenthesis are isolated yields. [c] Determined by $^1H$ NMR of crude product. [d] 5 mol% of catalyst. [e] 3.0 equivalents of **1a**. L = $(2,4\text{-}^tBu_2C_6H_3O)_3P$.

However, this hypothesis poses a considerable challenge, due to the preferential protonation of the gold enolate intermediate. To the best of our knowledge, if successful, this will be the first example of a gold–carbene[13] undergoing domino intermolecular C($sp^2$)–H functionalization and intramolecular aldol annulation.

To test this hypothesis, we began our study to examine the model reaction of 1-(3,5-dimethoxyphenyl)propan-2-one **1a** and phenyl α-diazoester **2a** in the presence of 10 mol% $PPh_3AuCl/AgNTf_2$ in dichloromethane (DCM) at rt. To our delight, the desired tandem C–H functionalization/aldol annulation product indanol **3aa** was obtained in good yield (76% NMR yield) with good diastereoselectivity (d.r. = 9 : 1, Table 1, entry 1) and exclusive *para* site-selectivity using a methoxyl group as the directing group. Several ligands were then screened to improve the efficiency and stereoselectivity. A significantly worse result was obtained using a more electron-rich N-heterocyclic carbene ligand (IPr) (entry 2). Tris(2,4-di-*tert*-butylphenyl) phosphite was finally identified to be the best ligand in terms of reactivity and diastereoselectivity, which furnished **3aa** in 81% NMR yield with 12 : 1 dr (entry 3). Low catalyst loading (5 mol%) did not affect the diastereoselectivity but decreased the yield (Table 1, entry 4). Increasing **1a** to 3 equivalents in conjunction with decreased loading of the catalyst (5 mol%) provided the best result (Table 1, entry 5). The use of $AgNTf_2$ alone gave the indanol **3aa** in 38% yield and the dimerization of carbene was the major product (Table 1, entry 6). It can be noted that the reaction catalyzed by other commonly-used catalysts did not afford **3aa** and gave only the dimerization of carbine. Other gold catalysts, silver salts, and solvents failed to give better results (Table S1, ESI†).

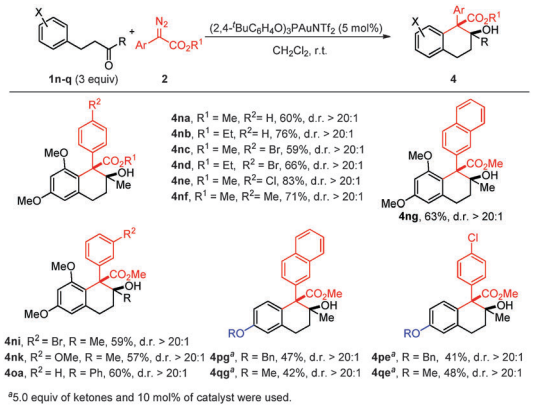
With optimal reaction conditions in hand, we next investigated the substrate scope of this gold-catalyzed cascade reaction and the results are summarized in Scheme 2. First, a series of alkyl and aryl ketones were prepared and tested for this cascade process. Compared to methyl ketones **1a**, substrates with butyl, cyclopropyl and phenyl groups, deliver the corresponding products **3ba–3ga** as a single isomer. Moreover, this cascade reaction shows good functional group tolerance. For example, the reactions of substrates with chloride, OTBS, allyl group and cyclopropane at the side chain proceeded quite well and delivered the




Scheme 2 Synthesis of indanols.

corresponding products **3ca–3ga** in moderate to good yields with excellent diastereoselectivities. It is also noteworthy that no cyclopropanation reaction of diazo compounds with allyl groups occurs (**3ea**),[14] which is consistent with our previous investigation.[9a] Gratifyingly, the cyclic ketone is also applicable to this process and the desired fused tricyclic products **3ha** and **3hc** were obtained in moderate yields with high d.r. Furthermore, methoxy, OTBS, OAllyl, OMOM, and OBn groups could be well introduced to the aryl moiety of the indanol products **3ia–3ma**, which are easily converted to other functional groups. Unfortunately, the reaction of phenol and aniline derivatives with **2a** obtained the dimmers of diazoester as the major products (ESI†).

We then investigated the scope of diazoesters **2** for this transformation (Scheme 2). Pleasingly, the reaction of ketone **1a** with various α-aryl α-diazoesters **2** worked quite well, diastereoselectively furnishing the desired indanols **3ab–3ak** in moderate to good yields. The reactions involving the diazoesters **2** with methyl groups showed more reactivity and delivered better diastereoselectivity than those bearing ethyl groups (**3aa** *vs.* **3ab**, **3ac** *vs.* **3ad**), which indicates that the steric hindrance of the ester moiety has a negative effect on this transformation. Moreover, diazooxoindoles **2l** are also applicable to the present transformation, producing the spiro product **3al** in good yield (80%). This transformation provided an alternative access to spiro-oxoindoles containing an all-carbon quaternary center, which is an essential motif in numerous natural products.[15]

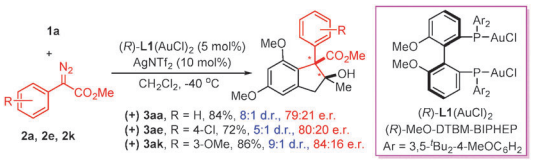



Scheme 3 Synthesis of tetrahydronaphthalenols.

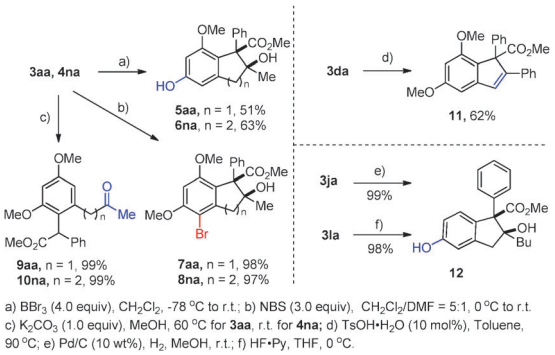
Having successfully realized the synthesis of indanols *via* gold-catalyzed tandem C–H functionalization/aldol reactions, we attempted to construct tetrahydronaphthalenols. Ketones **1n–1q** were prepared and treated with α-aryl α-diazoesters **2** under the abovementioned optimal reaction conditions. Gratifyingly, the reactions of **1n–1q** with various diazoesters **2** successfully delivered the desired products, tetrahydronaphthalenol derivatives **4na–4qe**, in moderate to good yields (Scheme 3). It must be noted that only a single stereoisomer was obtained in all cases. Compared to the abovementioned reaction of indanols, the yields in the tetrahydronaphthalenols synthesis were lower, which were attributed to the formation of a small amount of side products *via* direct C–H functionalization. It is quite interesting that this type of side product was not observed in the indanols synthesis.

A preliminary but promising result was obtained for the attempt on the asymmetric version of this gold-catalyzed tandem reaction. By the use of the (*R*)-MeO-DTBM-BIPHEP ligand, the reaction of ketone **1a** and diazoester **2a** furnished the indanol **3aa** in 84% yield with 79 : 21 e.r. (Scheme 4). Reasonable results were also obtained for diazoesters **1e** and **1k** with different substituents at different positions. Despite the fact that these results are not satisfactory, they prove that this cascade reaction is amenable to the enantioselective construction of two continuous chiral quaternary stereocenters.

To further showcase the synthetic applications of this methodology, we carried out several further transformations of some representative indanol and tetrahydronaphthalenol products (Scheme 5). The remote methoxyl groups of **3aa** and **4na** were selectively demethylated to obtain the corresponding **5aa** and **6na**. Regioselective bromation of **3aa** and **4na** with NBS led to mono-bromo-substituted **7aa** and **8na**. The structure and regioselectivity of **7aa** and **8na** were established by single crystal

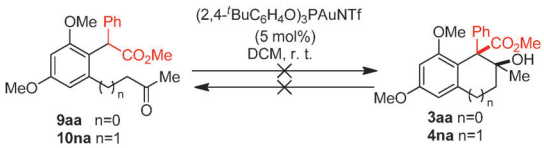



Scheme 4 Preliminary investigation on the asymmetric version.




Scheme 5 Synthetic applications.

X-ray diffraction analysis.[16] Moreover, ring-opening products **9aa** and **10na** were obtained in almost quantitative yield *via* a retro-aldol reaction when **3aa** and **4na** were exposed to $K_2CO_3$ in methanol. The elimination of **3da** smoothly obtained **11** in 62% yield. It should note that the corresponding phenol derivative **12** could be obtained easily *via* the deprotection of **3ja** and **3la** in quantitative yield, thus addressing the low reactivity issue of phenol derived ketones with the diazoesters.

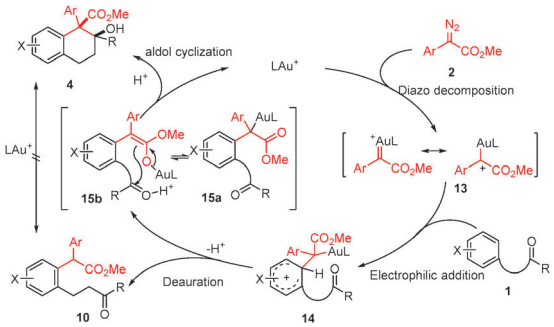



(1)

Because **10na**, *via* direct C–H functionalization, was observed as a side product in the tetrahydronaphthalenol synthesis, we wondered whether **9** and **10** would be the key intermediate to afford the target product **3** and **4**. However, no aldol reaction occurred under the reaction conditions we used (eqn (1)), which indicates that **9** and **10** were not the active intermediate for the aldol reaction. Moreover, the retro-aldol reaction also did not occur under the same conditions.

Based on the abovementioned experiments and previous reports, a plausible reaction pathway that accounts for the observation is proposed (Scheme 6). The electrophilic gold carbene **13**, which is *in situ* generated from the decomposition of the diazoester, would react with the aryl moiety of **1** to afford the gold-contained cationic intermediate **14**.[17] The deauration of **14** would obtain the C–H functionalization product **10**, whereas aromatization of **14** would afford tautomerized intermediates **15a** or **15b**, which undergo aldol cyclization to produce the target product **4** (for more details of the mechanism, see the ESI†).

In summary, we have developed a novel and efficient cascade strategy consisting of C–H functionalization and aldol cyclization for the construction of two adjacent quaternary centers, which provide facile access to indanols and tetrahydronaphthalenols in moderate to good yield with good diastereoselectivity. The preliminary results show that this process is amenable to asymmetric catalysis. The salient features of this reaction include readily available starting materials, mild conditions, good functional-group tolerance and easy further transformations of the products. This study would shine some light on the design of




Scheme 6 Proposed mechanism.

novel cascade reactions by trapping gold-contained active species *via* gold carbene-initiated reactions.

*Note added after first publication*: This article replaces the version published on 4th January 2016, which contained errors in the schemes presented in Table 1 and eqn (1).

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