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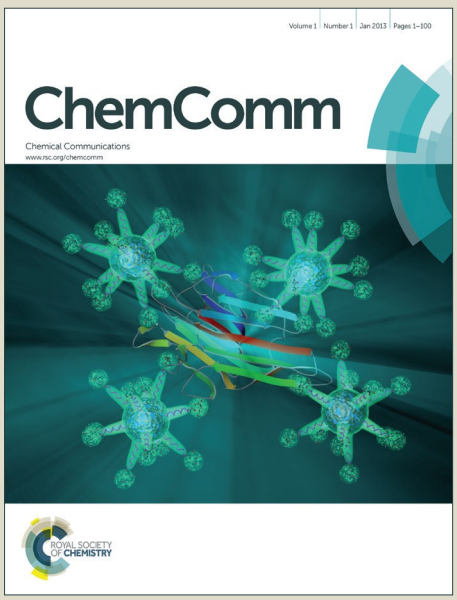

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Gold-Catalyzed Construction of Two Adjacent Quaternary Stereocenters via Sequential C-H Functionalization and Aldol Annulation

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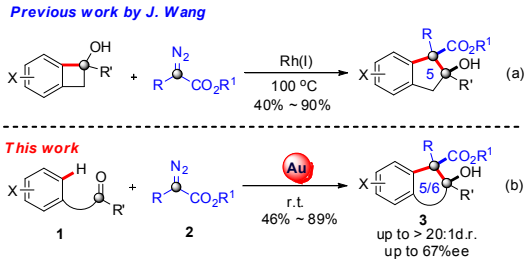
Zhunzhun Yu,[a] Haile Qiu,[a] Lu Liu*[a] and Junliang Zhang*[a,b]

A novel and efficient gold-catalyzed intermolecular C(sp^2)-H functionalization (Fiedel-Crafts alkylation) and aldol annulation strategy was presented. This cascade process allowed synthesizing a series of indanol and terahydronaphthalenol derivatives with two adjacent quaternary stereocenters. The reaction features with readily available starting materials, good diastereoselectivity, nice functional-group tolerance and mild reaction conditions. Furthermore, the preliminary result indicated 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, developing novel methods to efficiently construct quaternary carbon center,[2] especially the all-carbon one, has received considerable attention recently. Although numerous efforts have been devoted to this field, the efficient construction of these special units still remains vital challenge due to the steric congestion. The efficient C-C bond formation is believed to be the key issue for 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 center involving C-H bond functionalization would be highly desirable. Ideally, such an approach requires finishing in one convenient operation, mild conditions, functional-group tolerance and the use of readily available starting materials.

Yet, the carbene transfer reaction of diazo compounds catalyzed by transition-metal complexes, such as rhodium,



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

copper, silver, palladium, etc. represents one of the most effective approaches to not only C–H functionalization[4,5] but also construction of all-carbon quaternary center in recent years. Recently, Liang, Yu and Wang demonstrated transition-metal-catalyzed cascade reactions involving diazo compounds to access all-carbon quaternary center 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 have 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 novel process for efficient construction of these key motifs from more readily available precursors. Inspired by our and Shi's recent work[9] on gold-catalyzed[10] aromatic C-H functionalization with diazoesters[11], we assumed that these indanols and tetrahydronaphthalenols might rapidly constructed from much more readily available compounds **1** and diazoesters **2** by the combination of gold-catalyzed aromatic C-H functionalization and aldol reaction.[12] However, this hypothesis poses considerable challenge, due to the preferential protonation of the gold enolate intermediate. To the best of our knowledge, if success, it will be the first

[a] *Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, 3663 N. Zhongshan Road, Shanghai 200062, China, E-mail: lliu@chem.ecnu.edu.cn; jlzhang@chem.ecnu.edu.cn*
[b] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, CAS, 345 Lingling Road, Shanghai 200032, China*

† Footnotes relating to the title and/or authors should appear here.
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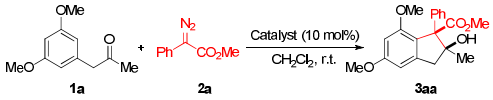
example of a gold-carbene[13] undergoing domino C(sp^2)-H functionalization and intermolecular aldol annulation.

Table 1. Optimization of reaction conditions.[a]

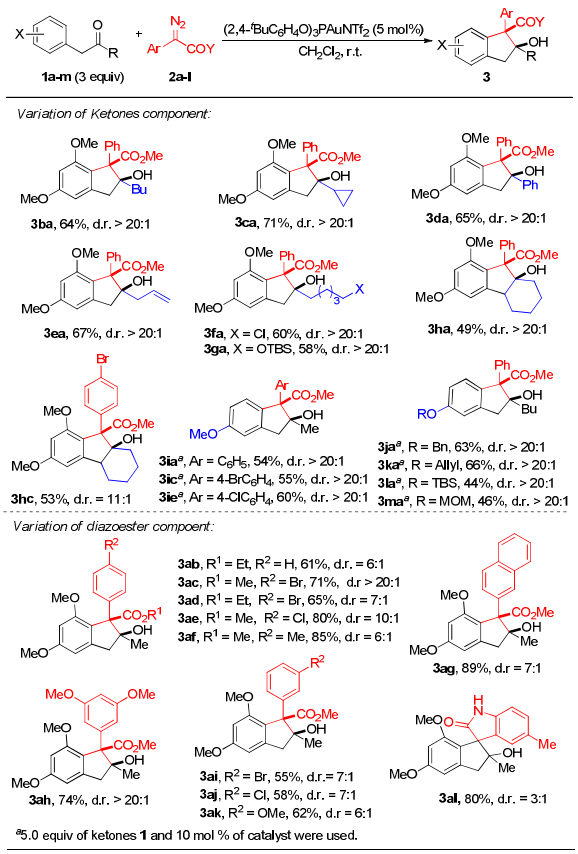


Entry	Catalyst	Time	Yield[b] (%)	d.r.[c]
1	$PPh_3AuCl/AgNTf_2$	45 min	76	9:1
2	$IPrAuCl/AgNTf_2$	45 min	48	>20:1
3	$LAuCl/AgNTf_2$	45 min	81	12:1
4[d]	$LAuCl/AgNTf_2$	45 min	68	11:1
5[d,e]	$LAuCl/AgNTf_2$	45 min	82 (76)	14:1
6	$AgNTf_2$	45 min	38	5:1

[a]The reaction was carried out with **1a** (0.3 mmol), **2a** (0.2 mmol), 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 equiv of **1a**. L = $(2,4\text{-}^tBu_2C_6H_3O)_3P$

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** came out 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 directing group. Several ligands were then screened to improve the efficiency and stereoselectivity. A significantly worse result was obtained by using 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, furnishing 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). Notable, the reaction catalyzed by other commonly-used catalysts cannot afford **3aa** but gave only the dimerization of carbene and other gold catalysts, silver salts, and solvents failed to give better results (Supporting information, table S1).

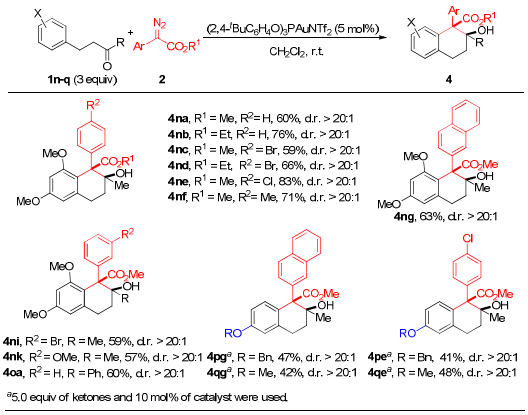
With optimal reaction conditions in hand, we next investigated the substrate scope of this gold-catalyzed cascade reaction. The results are summarized in Scheme 2. Firstly, a series of alkyl and aryl ketones are prepared and tested to this cascade process. Compared to methyl ketones **1a**, substrates with butyl, cyclopropyl and phenyl groups, deliver the corresponding products **3ba-3ga** as a single isomer. Besides, 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, delivering the 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 group takes place (**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, that methoxy, OTBS, OAllyl, OMOM, OBn groups could be well introduced to aryl moiety of the indanol products **3ia-3ma**, which are easily to be converted to the other functional groups. Unfortunately, the reaction of phenol and aniline derivatives with **2a** gave the dimmers of diazoester as the major products (Supporting Information).



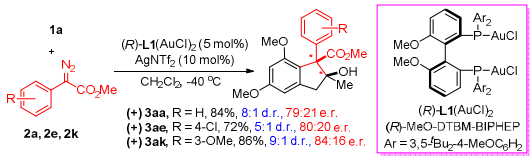
Scheme 2. Synthesis of indanols.

We then turned to investigate 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 group show more reactivity and deliver better diastereoselectivity than those bearing ethyl group (**3aa** vs **3ab**, **3ac** vs **3ad**), indicating that the steric hindrance of ester moiety has negative effect on this transformation. Meanwhile, 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 all-carbon

quaternary center, which is an essential motif in numerous natural products.[15]

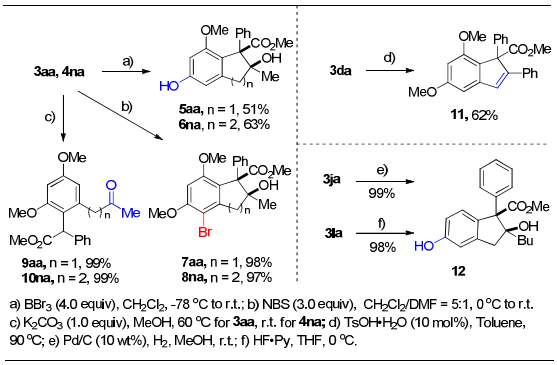


Scheme 3. Synthesis of tetrahydronaphthalenols.



Scheme 4. Preliminary investigation on asymmetric version.

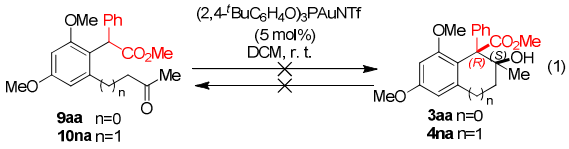
Having successfully realized the synthesis of indanols via gold-catalyzed tandem C-H functionalization/aldol reactions, we attempted to construct tetrahydronaphthalenols. Ketones **1n-1q** were prepared and treated with α-aryl α-diazoesters **2** under the above optimal reaction conditions. Gratifyingly,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



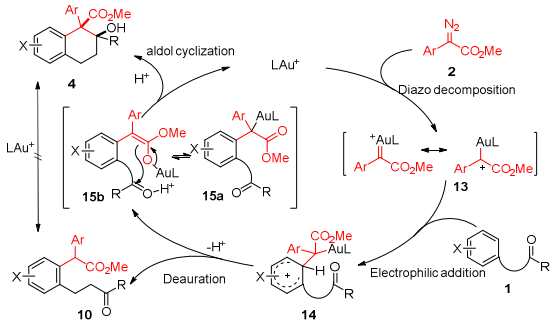
Scheme 5. Synthetic Applications.

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

To further showcase 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 give the corresponding **5aa** and 6na. Regioslective bromation of **3aa** and **4na** with NBS lead to mono-bromo-substituted **7aa** and **8na**. The structure and regioselectivity of **7aa** and **8na** were established by the single crystal X-ray diffraction analysis.[16] Meanwhile, ring-opening products **9aa** and **10na** were obtained in almost quantitative yield via retro-aldol reaction when the **3aa** and **4na** were exposed to K_2CO_3 in methanol. The elimination of **3da** smoothly gives **11** in 62% yield. It should note that the corresponding phenol derivative **12** could be obtained easily via deprotection of **3ja** and **3la** in quantitative yield, and thus addressing the low reactivity issue of the phenol derived ketones with the diazoesters.



Because **10na** via direct C-H functionalization were observed as side product in 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 takes place under the reaction conditions we used (eq 1), indicating **9** and **10** were not the active intermediate for the aldol reaction. Meanwhile, the retro-aldol reaction also does not occur under the same condition.



Scheme 6. Proposed mechanism.

Based on the above experiments and previous reports, a plausible reaction pathway that account for the observation is proposed (Scheme 6). The electrophilic gold carbene **13**, in-situ

generated from the decomposition of diazoester, would react with aryl moiety of **1** to afford gold-contained cationic intermediate **14**.[17] The deauration of **14** would give the C-H functionalization product **10**, while aromatization of **14** would afford tautomerized intermediates **15a** or **15b**, which undergo aldol cyclization to produce the target product **4** (For more details of mechanism, see Supporting Information).

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 a facile access to indanols and tetrahydronaphthalenols in moderate to good yield with good diastereoseletivity. A preliminary result showed 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 work would shine some light on design of novel cascade reaction by trapping gold-contained active species via gold carbene-initialled reaction.

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