Diazo Compounds

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Highly *para*-Selective C–H Alkylation of Benzene Derivatives with 2,2,2-Trifluoroethyl α-Aryl-α-Diazoesters

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Abstract: *Compared to the most popular directing-group-assisted strategy, the "undirected" strategy for C–H bond functionalization represents a more flexible but more challenging approach. Reported herein is a gold-catalyzed highly site-selective C(sp^2)–H alkylation of unactivated arenes with 2,2,2-trifluoroethyl α-aryl-α-diazoesters. This protocol demonstrates that high site-selective C–H bond functionalization can be achieved without the assistance of a directing group. In this transformation, both the gold catalyst and trifluoroethyl group on the ester of the diazo compound play vital roles for achieving the chemo- and regioselectivity.*

In the past century, the direct transformation of an unactivated carbon–hydrogen bond (C–H) to either a carbon–carbon or carbon–heteroatom (C–X) bond, termed C–H bond functionalization, has been a fundamentally important subject in organic and sustainable chemistry.[1] To make this strategy generally useful in organic synthesis, controlling site selectivity of inert C–H bonds has remained a key challenge. Substituted benzenes are ubiquitous motifs in nature, the synthetic world, and materials-related fields.[2] For example, they constitute the most frequently used skeleton in the small-molecule drugs listed in the FDA orange book.[3] Thus, the direct site-selective aromatic C–H functionalization of a benzene ring is highly important, especially for post-modification of bioactive compounds. The classic electrophilic aromatic substitution of monosubstituted unactivated arenes, such as toluene, introduced in textbooks for organic chemistry, may be the most common method used for aromatic C(sp^2)–H functionalization, but typically delivers mixtures of *ortho*- and *para*-substituted products.[4] Transition-metal-catalyzed, directing-group-assisted approaches have emerged as one of the most efficient and popular solutions to the site-selectivity problem.[5–7] A variety of directing groups (DGs) have been developed and widely utilized for *ortho* C(sp^2)–H functionalization, and in some cases for *meta* C(sp^2)–H functionalization[6] of arenes. Nonetheless, this approach is hardly applied to the *para* C(sp^2)–H bond functionalization,[7] especially for molecules lacking functional groups (e.g., alkyl-substituted benzenes). "Undirected" functionalization of C–H bonds, a strategy which involves the use of either a catalyst or reagent to control the site selectivity, is potentially more flexible but more challenging.[8] In most cases, the site selectivity is still a big issue, especially for monosubstituted unactivated arenes.[9,10] Therefore, the development of a general strategy for highly *para*-selective C(sp^2)–H functionalization of arenes, especially for monosubstituted arenes without a coordinating atom, would be highly desirable, and also requires conveniently operational steps, mild reaction conditions, high efficiency, broad substrate scope, low catalyst loading, and scalability.

The insertion of carbenes into C–H bonds has become an important aspect of undirected C–H functionalization.[11,12] However, the highly site-selective C(sp^2)–H functionalization of aryl rings of monoalkyl-substituted arenes remains elusive[13] because of the several competing reactions which occur when mixing an alkyl benzene with diazo esters in the presence of transition metals (Scheme 1a). For example, the groups of Pérez, Woo, and Dias reported that the Buchner reaction occurred under the catalysis of iron, silver, and copper complexes, respectively.[13a–c] Alternatively, the groups of Che and Davies demonstrated the rhodium-catalyzed benzylic C(sp^3)–H functionalization of toluene.[13d–e] Recently, the C(sp^2)–H functionalization of alkyl arenes was realized, but they produced a mixture of *ortho*-, *meta*-, and *para*-alkylation products.[13f–g] Herein, we wish to present our progress on the gold-catalyzed,[14] highly *para*-selective C–H functionalization of monoalkyl-substituted (aryl/halo) unactivated arenes (Scheme 1b).

Recently, a few examples of gold-catalyzed C–H functionalizations of activated arenes,[15] such as phenol, *N*-acylaniline, and anisole with α-diazoesters,[16] were developed. However, during the course of expanding the substrate scope to toluene, the desired *para*-C–H functionalization product **3aa** was obtained in very low yield (25%), even with slow addition of the methyl α-aryl-α-diazoacetate **2a** to toluene (**1a**), thus delivering the dimer of **2a** as the major product (Table 1, entry 1). Further attempts to screen other gold catalysts and metal catalysts did not address the low yield and bad selectivity, and the best result was obtained when the reaction was catalyzed by $(2,4\text{-}t\mathrm{Bu}_2\mathrm{C}_6\mathrm{H}_3\mathrm{O})_3\mathrm{PAuPhCNSbF}_6$ (entry 3). We assumed that the low nucleophilicity of toluene might account for the low yield of C–H functionalization and thus the dimerization reaction occurs. Given the fact that we could not change this inherent low reactivity of toluene and inspired by gold-stabilized carbocation species[6b,17,18] as the key intermediate, we envisaged that the enhancement of the electrophilicity of the gold carbocation species, by installing an electron-withdrawing group on the ester group of

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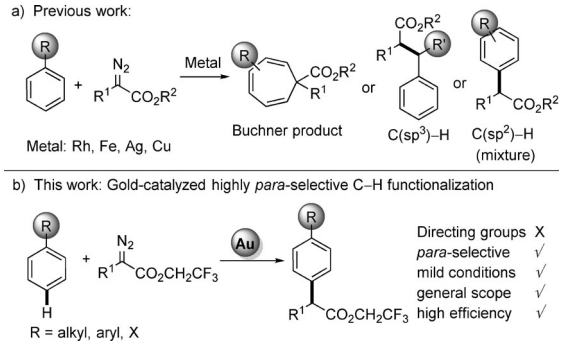


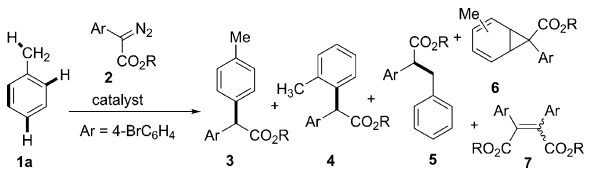
Scheme 1. The reaction of monosubstituted arenes and diazo esters.

α-diazoesters, may provide an opportunity to address the low efficiency. Given this hypothesis, diazo esters with electron-withdrawing groups, instead of a methyl group, were prepared and tested (entries 4–6). To our delight, the C–H functionalization product **3ad** was isolated in 82% yield when the trifluoroethyl α-aryl-α-diazoester **2d** was used as the substrate (entry 6; standard reaction conditions). A series of other metal catalysts, such as Rh, Ru, Cu, Fe, and others, which are commonly used in carbene transfer, were employed, and diverse products arising from either benzylic C–H insertion, cyclopropanation, Buchner reaction, *ortho*-C–H functionalization, or diazo coupling, were detected (entries 7–9 and Table S1 in the Supporting Information). These results clearly indicated that the gold catalyst displayed a unique selectivity compared to other metal catalysts. Gratifyingly, this transformation proceeds smoothly, even with the use of only 2 equivalents of toluene, in CH_2Cl_2 (entry 10).

To explore the substrate scope, a variety of trifluoroethyl α-aryl diazoesters (**2a**–**n**) were prepared and examined (Table 2).The exclusive *para* C(sp^2)–H functionalization products **3ae**–**an** were isolated in good to excellent yields. It is noteworthy that none of the products derived from benzylic C(sp^3)–H insertion or *ortho*-, *meta*-C(sp^2)–H functionalization, or Buchner reaction were detected. Furthermore, a gram-scale reaction using 1.1 grams of **2e** and **1a** also works well, even with a much lower catalyst loading (0.5 mol%), thus furnishing 1.12 grams of the corresponding product **3ae** in 83% yield.

We then examined a variety of substituted benzenes (Table 3). The reactions of either monoalkyl- or monoaryl-substituted arenes (**1b**–**e**) with **2a** proceeded smoothly, thus affording moderate to excellent yield of the corresponding *para*-selective C–H functionalization products **3bi**–**ei**. Notably, the reaction of the arene equipped with an allyl substituent could give the *para* C–H bond alkylation product **3fj** without detection any product by either cyclopropanation or secondary C(sp^3)–H insertion of the doubly activated benzyl position, thus indicating that this approach is highly chemo- and regioselectivity. Of course, bialkyl- and trialkyl-substituted benzene are also compatible in this transformation, and deliver the corresponding site-selective alkylation products **3gi**–**ji**. Next, we wondered if the reaction could be conducted in the presence of arenes with heteroatoms

Table 1: Optimization of reaction conditions.[a]

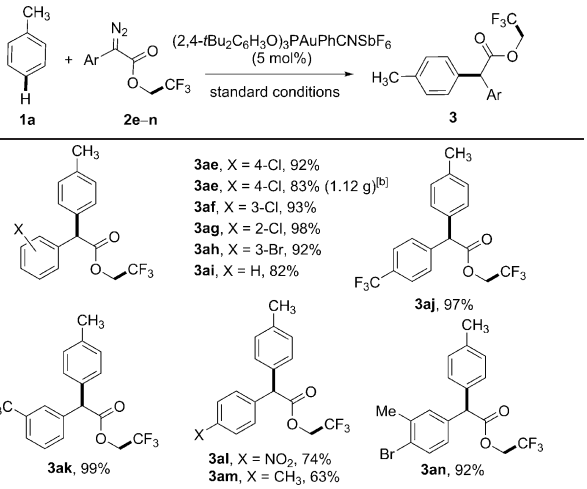


Entry	R (**2**)	Catalyst (5 mol%)	Yield [%][b] **3**/**4**/**5**/**6**/**7**
1	Me (**2a**)	**L**AuSbF_6	(25):0:0:0:(57)
2	Me (**2a**)	Ph_3PAuSbF_6	trace:0:0:0:85
3	Me (**2a**)	**L**AuPhCNSbF_6	45:0:0:0:46
4	CH_2CCl_3 (**2b**)	**L**AuPhCNSbF_6	(72):(3):0:0:10
5	CH_2CBr_3 (**2c**)	**L**AuPhCNSbF_6	(70):(0):0:0:12
6	CH_2CF_3 (**2d**)	**L**AuPhCNSbF_6	(87):0:0:0:(5)
7	CH_2CF_3 (**2d**)	Rh$(OAc)_2$	0:0:(57):0:(18)
8[c]	CH_2CF_3 (**2d**)	Fe$(OTf)_2$	15:4:9:43:0
9	CH_2CF_3 (**2d**)	AgSbF_6	63:9:0:0:0
10[d]	CH_2CF_3 (**2d**)	**L**AuPhCNSbF_6	(76):0:0:0:(10)

[a] Unless otherwise noted, the solution of **2** (0.4 mmol) in 0.2 mL of toluene was introduced into catalyst (5 mol%) in toluene (0.4 mL) at room temperature by a syringe in 1 min and then being stirred for another 2 min. [b] Determined by NMR spectroscopy. The number within parentheses is the yield of the isolated product. [c] 110°C. [d] Toluene (2 equiv) was used in CH_2Cl_2 (1 mL). **L** = (2,4-*t*$Bu_2C_6H_3O)_3$P, Tf = trifluoromethanesulfonyl.

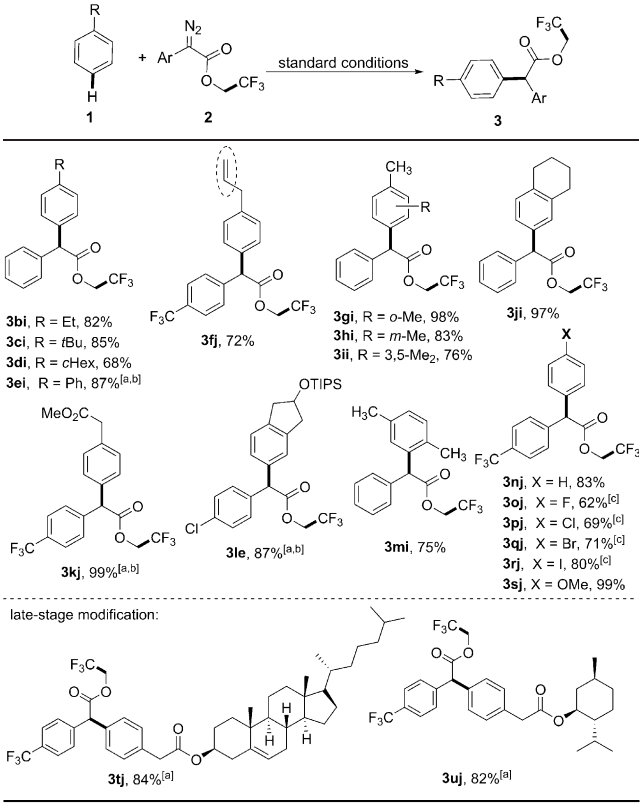
attached to the alkyl substituent. To our delight, ester and OTIPS groups are compatible with this *para* C(sp^2)–H alkylation reaction (**3kj** and **le**). When *p*-xylene was used, the reaction with a diazoester also delivered the *ortho* C–H bond functionalization product **3mi** in 75% yield. This result also demonstrates that this gold-catalyzed reaction of donor/acceptor carbenes has a strong preference for functionalization of aromatic C(sp^2)–H bonds instead of C(sp^3)–H bonds, even though the *para*-position is occupied. Gratifyingly,

Table 2: Scope with respect to diazo compounds.[a]



[a] Unless otherwise noted, a solution of **2** (0.4 mmol) in 0.2 mL of toluene was introduced to (2,4-*t*$Bu_2C_6H_3O)_3$PAuPhCNSbF_6 (5 mol%) in toluene (0.4 mL) at room temperature by a syringe over a period of 1 min and the reaction mixture stirred for another 2 min (standard conditions). [b] Used 0.5% catalyst.

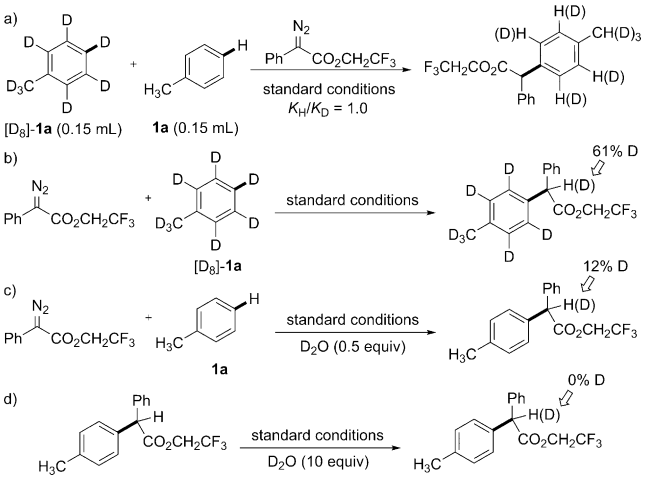
Table 3: Scope with respect to various arenes.[a]



[a] Used arenes (2 equiv) in CH_2Cl_2 (1 mL). [b] Used 7.5% catalyst. [c] Yield of the isolated alcohols resulting from C–H alkylation and reduction. TIPS = triisopropylsilyl.

simple benzene is also applicable to this process and the desired product **3nj** was obtained in 83% yield. To our surprise, halobenzenes (F, Cl, Br, I) could also selectively undergo the *para* C–H functionalization (**3oj**–**rj**). The electron-withdrawing nature of halogens may account for the slightly lower yield. It is not surprising to find that the reaction of an arene with an electron-donating group (OMe) could afford the *para*-selective product **3sj** in 99% yield. Furthermore, this strategy is applicable to late-stage modification of natural products or pharmaceutical compounds because of its operational convenience and mild reaction conditions. To our delight, a cholesterol derivative and a menthol derivative gave the *para*-selective C–H functionalization in 84 and 82% yield, respectively (**3tj** and **3uj**), and highlights the potential usage of this transformation for the screening of benzene-containing lead compounds. It should be emphasized that only 2 equivalents of the arene **1** were used and high yields of the corresponding *para*-selective C–H functionalization products **3** (e.g., **3kj**, **3rj**, **3tj**, **3uj**) were obtained.

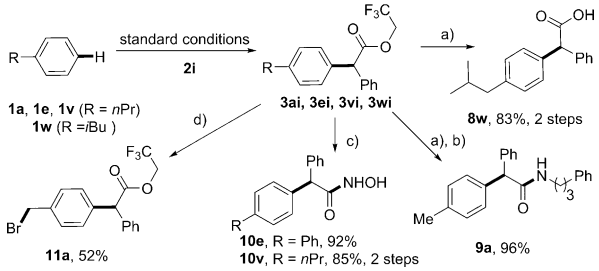
To gain mechanistic insight to the present transformation, several control experiments were carried out. The result of Scheme 2a shows that this transformation does not exhibit a kinetic isotope effect, thus indicating that the C–H bond cleavage for toluene is not involved in the rate-determining step. Additional control experiments demonstrate that water in the solvent participates in the reaction process as a proton



Scheme 2. Preliminary mechanism studies.

shuttle, and is consistent with our previous mechanistic study (Scheme 2b–d).[18]

Most importantly, this method may be useful for the facile synthesis of useful building blocks and bioactive compounds from readily available starting materials (Scheme 3). The



Scheme 3. Synthetic application. a) NaOH, MeOH, reflux, 2 h; b) 3-phenylpropylamine, HUAT, Et_3N, DMF, RT, 10 h; c) $NH_2OH{\cdot}HCl$, KOH, MeOH, RT, 3 h; d) $AuCl_3$, NBS, DCE, RT,30 h. DCE = 1,2-dichloroethane, DMF = *N*,*N*-dimethylformamide, HUAT = *o*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, NBS = *N*-bromosuccinimide.

analogue of ibuprofen, **8w**, the most widely used nonsteroidal anti-inflammatory drugs (NSAIDs), was prepared in 83% yield by the direct C–H functionalization and hydrolysis from readily available starting materials.[19a] The antiproliferative **9a** and the inhibitors (**10e** and **10v**) of histone deacetylase were efficiently accessed by amidation in good yields.[19b–c] Interestingly, the unexpected gold-catalyzed benzylic bromination of **3ai** was observed to deliver the product **11a** in 52% yield. The structure of **9a** was confirmed by single-crystal X-ray analysis.[20]

In summary, we have developed a novel gold-catalyzed highly *para*-selective C–H functionalization of unactivated arenes with 2,2,2-trifluoroethyl α-aryl-α-diazoesters, thereby directly generating synthetically useful diarylacetates with convertible functional groups in good yields under mild reaction conditions. A wide range of benzene derivatives are compatible with this new process. The salient features of this

simple, yet powerful, protocol includes readily available starting materials, mild reaction conditions, high efficiency, general substrate scope, and ease of scale-up. It should be an attractive and promising synthetic tool for the preparation of natural products and pharmaceuticals, especially in late-stage modifications. Moreover, this work would broaden the application of fluorinated diazoesters in organic synthesis and open a new door for the design of undirected C–H functionalization. Further investigations of the site-selective aromatic C–H functionalization with diazo compounds are underway.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: arenes · C–H activation · diazo compounds · gold · homogeneous catalysis

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[20] CCDC 1508516 (**9a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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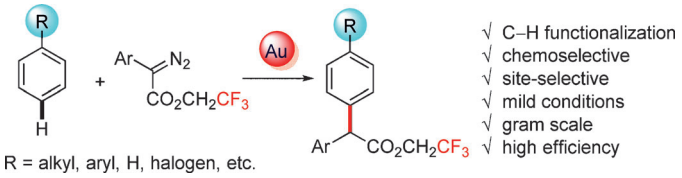
Communications

Diazo Compounds

B. Ma, Z. Chu, B. Huang, Z. Liu, L. Liu,* J. Zhang* ——— ■■■–■■■

Highly *para*-Selective C–H Alkylation of Benzene Derivatives with 2,2,2-Trifluoroethyl α-Aryl-α-Diazoesters



Convertible: A highly *para*-selective, gold-catalyzed C–H functionalization of unactivated arenes with 2,2,2-trifluoroethyl α-aryl-α-diazoesters is reported. The resulting products are produced in good yields under mild reaction conditions, and are synthetically useful diarylacetates containing convertible functional groups.

