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Direct synthesis of anthracenes from *o*-tolualdehydes and aryl iodides through Pd(II)-Catalyzed sp^3 C–H arylation and electrophilic aromatic cyclization

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ABSTRACT

The first direct synthesis of substituted anthracenes from o-tolualdehydes and aryl iodides *via* a Pd(II)-catalyzed C–H arylation using an alcohol-bearing transient directing group and subsequent AgOTf-assisted electrophilic aromatic cyclization is described. New transient directing groups consisting of amino acids and amino alcohols enhanced the reactivity, and the C–H arylation was complete in 12 h at 90 °C. By simply changing the silver salt to silver triflate, the one-pot synthesis of anthracene derivatives was carried out using the present reaction conditions.

1. Introduction

Anthracenes have attracted the attention of many chemists by virtue of their broad utility.[1] They can be utilized as chromophores in various kinds of bio-probes[2] or light-emitting devices[3] and as starting materials or reagents in syntheses of multifunctional metal-organic frameworks[4] or potential polycyclic aromatic drugs.[5] Their versatility has made the development of efficient methods for their formation highly desirable. A number of synthetic methods for the preparation of anthracenes have been reported. However, those traditional synthetic strategies, such as Bronsted acid-catalyzed dehydrative cyclizations,[6] Au-catalyzed cyclizations of o-alkynyldiarylmethanes,[7] [4 + 2] cycloadditions with naphthoquinones or benzynes,[8] and Co-catalyzed [2 + 2+2] alkyne-cyclotrimerizations,[9] usually require complex substrates that demand multistep syntheses and show poor functional group tolerance. The recent advances in transition metal-catalyzed C–H functionalization inspired us to develop a direct synthetic method for the preparation of substituted anthracenes from easily accessible chemicals. Transition metal-catalyzed C–H functionalizations have undoubtedly become one of the most direct synthetic strategies[10] and have provided many efficient synthetic routes for total syntheses of natural products.[11] A directing group (DG) in a substrate, such as a pyridine, an imine, an amine, a (thio)amide, or a carboxylate, are essential in C–H activation strategies to lower the activation energy *via* the formation of a five- or six-membered metallacycle.[12] However, requiring a DG hurts the step- and atom-economy of the synthesis of a target compound by adding synthetic steps for DG installation[1] and DG detachment.[13] The emergence of transient directing groups (TDGs) has become a crucial breakthrough for alleviating the intrinsic problems of DG-promoted C–H activations. Since Jun's group reported Rh-catalyzed sp^2 C–H functionalization with transient amino ligands,[14] many relevant studies have been reported.[15] In the case of sp^3 C–H functionalizations, Yu and co-workers first reported a synthetic protocol for the preparation of 2-benzylbenzaldehydes by Pd-catalyzed alkyl C–H activation using an amino acid as a TDG.[16] Later, the related reports of sp^3 C–H functionalization using a TDG strategy have been published by several groups in 2017, respectively.[17]

To construct tricyclic aromatic compounds like anthracenes,

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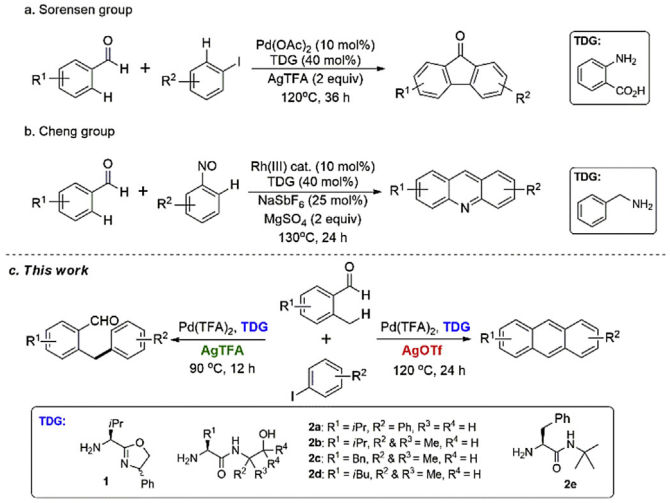
Sorensen and co-workers used benzaldehydes and aryl iodides with 40 mol% anthranilic acid as a TDG to obtain fluorenones *via* a Pd-catalyzed *ortho* C–H arylation and migratory insertion (Scheme 1-a).[15c] An approach to the preparation of substituted acridines by Rh(III)-catalyzed C–N bond formation *via ortho* C–H activation controlled by benzyl amine as a TDG and subsequent electrophilic aromatic cyclization has also been reported (Scheme 1-b).[15a] Inspired by these elegant strategies, we hypothesized that a similar approach would be applicable for the one-pot synthesis of substituted anthracenes by an sp^3 C–H arylation using a TDG and subsequent electrophilic aromatic cyclization (Scheme 1-c). In contrast to the acridine synthesis, a benzene moiety is less reactive than an aniline moiety towards electrophilic aromatic cyclization, so a Lewis acid additive is essential to obtain the final product. In this sense, we studied the efficient synthesis of *o*-benzylbenzaldehydes with a TDG-assisted sp^3 C–H arylation strategy as well as the one-pot synthesis of anthracenes. To the best of our knowledge, there have been no reports on the direct synthesis of anthracenes from simple starting materials.

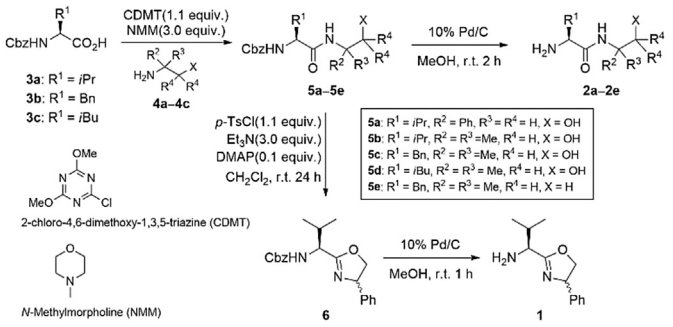
2. Results and discussion

To obtain *o*-benzylbenzaldehydes by an efficient sp^3 C–H arylation, we assumed that oxazoline-bearing primary alkylamine **1** would be the best TDG to accelerate the oxidative addition of the Pd(II) intermediate to the aryl iodide due to the strong σ-donating ability of the oxazoline moiety. Moreover, oxazoline-based TDGs have advantages including easy installation of the chiral fragment and simple synthesis from Cbz-protected natural amino acids (valine **3a**, phenylalanine **3b**, and leucine **3c**) and amino alcohols (DL-phenylglycinol **4a**, 2-amino-2-methylpropanol **4b**, and *tert*-butylamine **4c**); including CDMT-mediated amide synthesis for **5**, **5a**–**5e**,[18] oxazoline formation under basic condition for **6**, and deprotection of Cbz moiety by hydrogenolysis for **1** and **2a**–**2e** (Scheme 2).

Based on this strategy, we commenced our study by treating *o*-tolualdehyde (**7a**) with *p*-iodophenol (**8a**), TDG **1**, and the Pd catalyst. The reaction generated arylated product **9a** in 50% yield in 36 h. We also observed that the ring opening of oxazoline **1** occurred under the reaction conditions, and δ-amino alcohol **2a** was regenerated since the reaction is conducted under acidic conditions. To clarify that the active TDG is either **1** or **2a**, an sp^3



Scheme 1. Direct Synthesis of Tricyclic Aromatic Compounds *via* TDG-assisted C–H activation strategies.

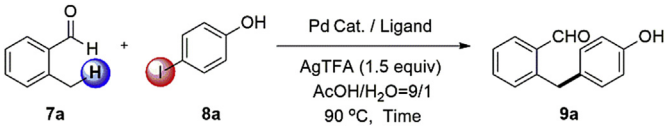


Scheme 2. Preparation of TDGs **1** and **2a**–**2e**.

C–H arylation reaction with **2a** was conducted, and it was found that **2a** allowed a comparable yield (48%) to oxazoline-based TDG **1**. As a result, we have modified the TDG strategy from oxazoline derivatives to alcohol-bearing, amino acid-amino alcohol coupled molecules as novel TDGs.

We have successfully synthesized a series of amino acid-amino alcohol coupled TDGs (**2a**-**2d**) by a simple, 3-step procedure from an easily accessible Cbz-protected amino acid. In addition, at the outset of our studies, *o*-tolualdehyde (**7a**) and 4-iodophenol (**8a**) were used as model substrates in the presence of various catalytic palladium systems (Table 1). A low conversion was observed in the absence of a TDG after a short time (entry 1). The addition of a transient group increased the efficiency of the reaction (entries 3–5), and the structure of the employed amino acid-based TDGs impacted the activity of the palladium catalyst. Among the three representative amino acid derivatives (**2b**, **2c**, and **2d**), phenylalanine-based TDG **2c** showed the best conversion in the sp^3 C–H arylation. To verify the role of the hydroxyl group of **2c**, a CH_3-substituted TDG (**2e**), instead of $-CH_2OH$, was employed in the Pd-catalyzed reaction. In the absence of a terminal alcohol group (**2e**),

Table 1
Optimization of the reaction conditions for the palladium-catalyzed sp^3 C–H arylation.[a]



Entry	Cat. (mol%)	TDG (mol%)	Time (h)	Yield[b] (%)
1	$Pd(OAc)_2$ (10)	–	6	0
2	$Pd(OAc)_2$ (10)	**1**	36	50
3	$Pd(OAc)_2$ (10)	**2a**, Val-PhAA (40)	36	48
4	$Pd(OAc)_2$ (10)	**2b**, Val-Me_2AA (40)	36	50
5	$Pd(OAc)_2$ (10)	**2c**, Phe-Me_2AA (40)	36	59
6	$Pd(OAc)_2$ (10)	**2d**, Leu-Me_2AA (40)	36	43
7	$Pd(OAc)_2$ (10)	**2e**, Phe-AM-*t*Bu (40)	36	25
8	$Pd(TFA)_2$ (10)	–	6	0
9	$Pd(TFA)_2$ (10)	**2c**, Phe-Me_2AA (40)	6	60
10	$Pd(TFA)_2$ (10)	**2c**, Phe-Me_2AA (40)	12	81 (63[f])
11	$Pd(TFA)_2$ (15)	**2c**, Phe-Me_2AA (40)	6	77
12[c]	$Pd(TFA)_2$ (10)	**2c**, Phe-Me_2AA (40)	12	35
13[d]	$Pd(TFA)_2$ (10)	**2c**, Phe-Me_2AA (40)	12	29
14[e]	$Pd(TFA)_2$ (10)	**2c**, Phe-Me_2AA (40)	36	<10

[a] All reactions were performed with 0.2 mmol (1 equiv.) of **8a** and 0.24 mmol of **7a**.
[b] The yield was determined by ^1H NMR analysis of the crude product using CH_2Cl_2 as the internal standard.
[c] Conditions: O_2 atmosphere
[d] Conditions: N_2 atmosphere
[e] 4-Bromotoluene was used instead of 4-iodophenol.
[f] Isolated yield.