Accepted Manuscript

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

Hyojin Park, Kwangho Yoo, Byunghyuck Jung, Min Kim

PII: S0040-4020(18)30249-7

DOI: 10.1016/j.tet.2018.03.006

Reference: TET 29346

To appear in: *Tetrahedron*

Received Date: 6 February 2018

Revised Date: 28 February 2018

Accepted Date: 4 March 2018

Please cite this article as: Park H, Yoo K, Jung B, Kim M, Direct synthesis of anthracenes from *o*-tolualdehydes and aryl iodides through Pd(II)-Catalyzed sp^3 CH arylation and electrophilic aromatic cyclization, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.03.006.

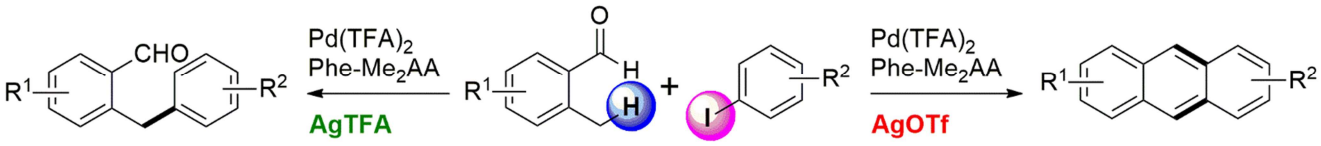
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Direct Synthesis of Anthracenes from *o*-Tolualdehydes and Aryl Iodides through Pd(II)-Catalyzed sp^3 C–H Arylation and Electrophilic Aromatic Cyclization

Leave this area blank for abstract info.

Hyojin Park,[a] Kwangho Yoo,[a] Byunghyuck Jung,*[,b] and Min Kim*[,a]
[a]*Department of Chemistry and BK21Plus Research Team, Chungbuk National University, Cheongju, 28644, Republic of Korea*
[b]*School of Basic Science, Daegu Gyeongbuk Institute of Science and Technology (DGIST), Daegu, 42988, Republic of Korea*



Tetrahedron
journal homepage: www.elsevier.com

Direct Synthesis of Anthracenes from *o*-Tolualdehydes and Aryl Iodides through Pd(II)-Catalyzed sp^3 C–H Arylation and Electrophilic Aromatic Cyclization

Hyojin Park,[a] Kwangho Yoo,[a] Byunghyuck Jung,[b,*] and Min Kim [a,*]

[a] *Department of Chemistry and BK21Plus Research Team, Chungbuk National University, Cheongju, 28644, Republic of Korea*
[b] *School of Basic Science, Daegu Gyeongbuk Institute of Science and Technology (DGIST), Daegu, 42988, Republic of Korea*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Transient directing groups
C–H activation
sp^3 C–H arylation
One-pot synthesis
Anthracenes

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

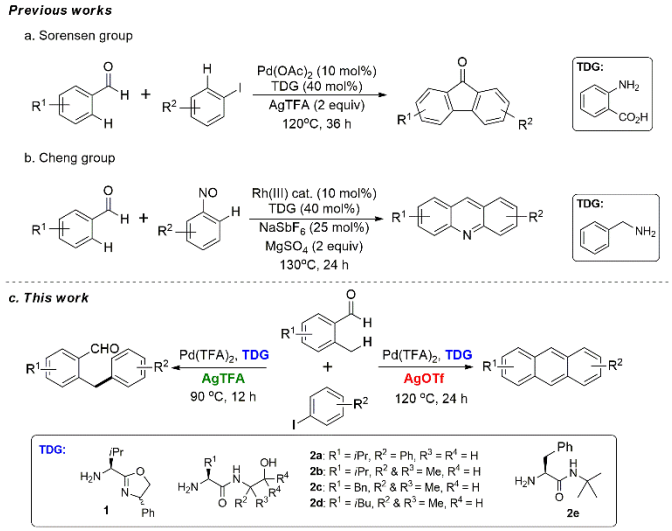
1. Introduction

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, 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

* Corresponding author. Tel.: +82-53-785-6625; fax: +82-53-785-6609; e-mail: byunghyuck.jung@dgist.ac.kr (B. Jung), minkim@chungbuk.ac.kr (M. Kim)

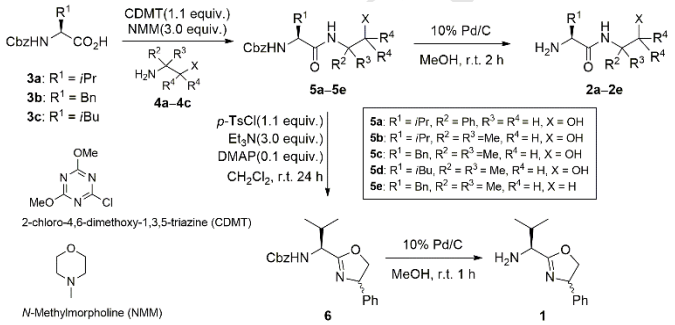
cyclization (Scheme 1-c). In contrast to the acridine synthesis, a benzene moiety is less reactive than an aniline moiety towards electrophilic aromatic cyclization, so a Lewis acid additive is essential to obtain the final product. In this sense, we studied the efficient synthesis of *o*-benzylbenzaldehydes 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.



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

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 deprotetion of Cbz moiety by



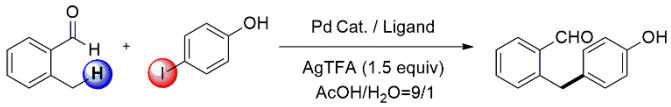
hydrogenolysis for **1** and **2a**–**2e** (Scheme 2).

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

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 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**), the conversion was lowest among the TDGs (entry 7). Further improvement was observed by changing the palladium catalyst precursor from palladium acetate ($Pd(OAc)_2$) to palladium trifluoroacetate ($Pd(TFA)_2$). Although no reactivity was observed with $Pd(TFA)_2$ alone at 90 °C for 6 h (entry 8), the addition of TDG **2c** resulted in a dramatic increase of the efficiently of the reaction and led to 81% of arylated product **9a** within 12 h at 90 °C (entry 10). It should be noted that the laboratories of Yu and Hu reported Pd(II)-catalyzed sp^3 C–H arylations of *o*-tolualdehyde and aryl iodide using TDGs; *glycine* was used by Yu's group and *acetohydrazide* was used by Hu's group.[16,19] Nevertheless, extended reaction times (24~36 h) and an elevated reaction temperature (110 °C) undermined the practicality of the method. In this sense, TDG **2c** could be one solution to making this system more practical. When the amount of palladium catalyst was further increased, the reaction time could be decreased to 6 h with good yield (entries 10 and 11). Interestingly, in this case, a N_2 or O_2 atmosphere reduced the efficiency of the reaction compared to a regular air atmosphere (entries 10, 12, and 13). Unfortunately, aryl bromide was inert under the reaction conditions (entry 14).

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



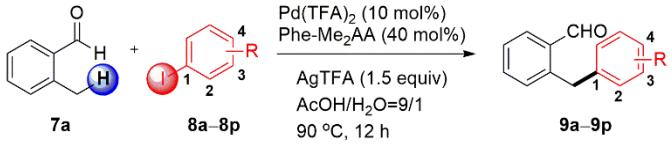
Entry	Cat. (mol%)	TDG (mol%)	Time (h)	Yield[b] (%)
1	$Pd(OAc)_2$ (10)	–	6	0
2	$Pd(OAc)_2$ (10)	**1**	36	50
3	$Pd(OAc)_2$ (10)	**2a**, Val-PhAA (40)	36	48
4	$Pd(OAc)_2$ (10)	**2b**, Val-Me_2AA (40)	36	50
5	$Pd(OAc)_2$ (10)	**2c**, Phe-Me_2AA (40)	36	59

6	$Pd(OAc)_2$ (10)	**2d**, Leu-Me_2AA (40)	36	43
7	$Pd(OAc)_2$ (10)	**2e**, Val-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 ^{1}H 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.

Under the optimized reaction conditions using 10 mol% $Pd(TFA)_2$ and 40 mol% Phe-Me_2AA (**2c**), a range of iodoarenes (**8a-8p**) were explored with *o*-tolualdehyde (**3a**) in the sp^3 C–H bond arylation (Table 2). Iodobenzenes **8b**, **8c**, and **8d** with simple non-coordinating substituents (–H or –Me) showed the best performance (87~91% yield). Coordinating substituents were detrimental to the efficiency (54~68% yield), but electronic variations of the substituents on the iodobenzenes did not have a substantial influence on the reaction efficiency (56% of **9f** vs 54% of **9p**). We observed that changes to the steric environment had significant effects on the sp^3 C-H bond arylation (43% of **9e**). In contrast to Ar–I, Ar–F and Ar–Cl were well tolerated in the Pd-catalyzed reaction and allow the preparation of fluoro- and chloroiodobenzene derivatives (**9l**, **9m**, and **9n**).

Table 2. Pd-catalyzed sp^3 C–H arylation with various iodobenzenes[a]

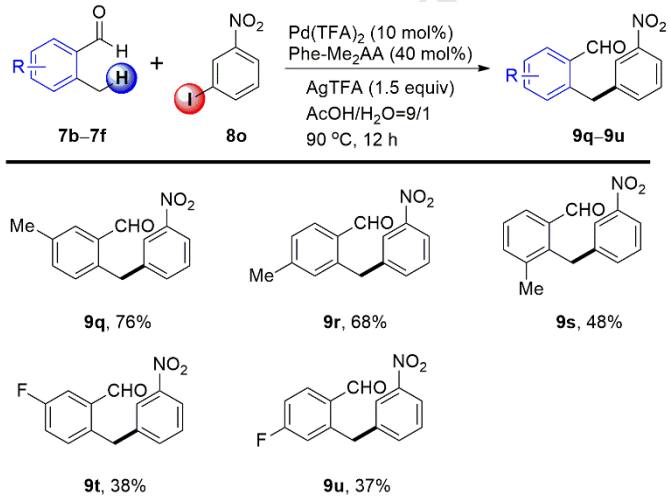


7a 8a–8p 9a–9p

Entry	R	Yield (%)[b]
1	4-OH	**9a**, 63
2	H	**9b**, 87[b]
3	3-Me	**9c**, 91[b]
4	4-Me	**9d**, 89[b]
5	2-OMe	**9e**, 43[b]
6	4-OMe	**9f**, 56[b]
7	4-Ac	**9g**, 55
8	3-CO_2H	**9h**, 68
9	4-CO_2H	**9i**, 66
10	3-CO_2Me	**9j**, 62
11	4-CO_2Me	**9k**, 59
12	3-F	**9l**, 63[b]
13	4-F	**9m**, 54[b]
14	4-Cl	**9n**, 62[b]
15	3-NO_2	**9o**, 54
16	4-NO_2	**9p**, 54

[a–b]see footnotes *a–b* of Table 1.

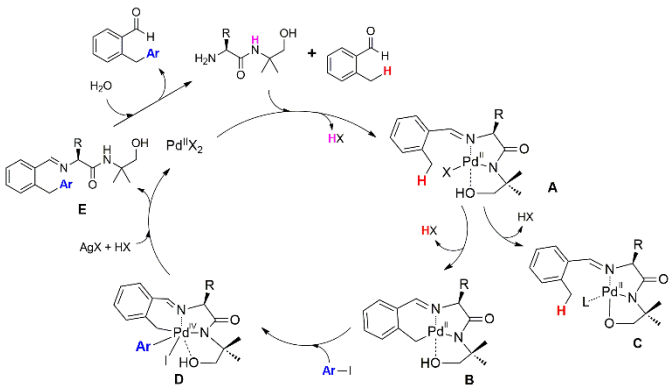
Next, the scope of benzaldehyde derivatives was examined in the reaction with 1-iodo-3-nitrobenzene (**8o**, Scheme 3). It was clearly that this palladium-catalyzed sp^3 C-H bond arylation is highly sensitive to the steric environment. 2,3-Dimethyl-substituted benzaldehyde showed a lower yield of the desired product than 2,4-dimethyl- or 2,5-dimethyl-substituted benzaldehydes (**9q**, **9r**, and **9s**). In addition, when an aldehyde with an additional fluoro substituent was subjected to the reaction conditions, the arylated product was isolated in moderate yield, which suggests electron-rich benzaldehydes are more favorable



in the present reaction conditions (Scheme 3).

Scheme 3. Pd-catalyzed sp^3 C-H arylation with various benzaldehydes.

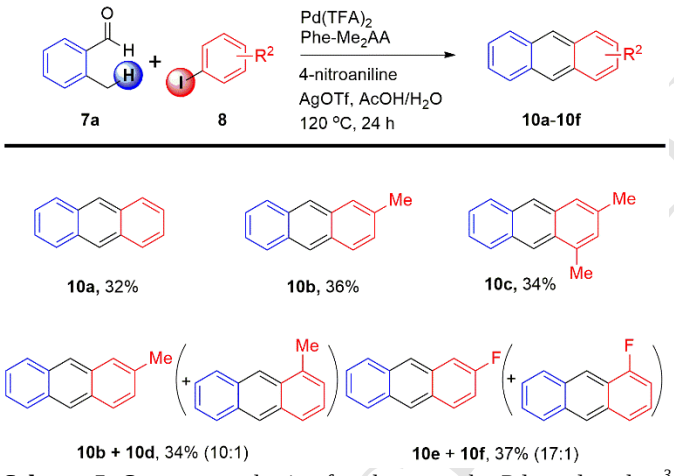
A putative reaction mechanism of the TDG-assisted sp^3 C–H arylation is proposed as shown in Scheme 4.[15c,20] The catalytic cycle begins with the formation of the transient directing group from an amino alcohol and *o*-tolualdehyde. After complexation of PdX_2 with the *in situ*-generated imine to form Pd(II)-complex **A**, the sp^3 C–H proximal to the metal center undergoes palladation with the loss of CF_3COOH.[21] Oxidative addition of Pd(II)-complex **B** to iodobenzene produces Pd(IV)-intermediate **D**,[22] and subsequent reductive elimination allows the formation of arylated imine **E** along with the regeneration of PdX_2 *via* a ligand exchange with AgTFA and trifluoroacetic acid (or acetic acid). Hydration of imine **E** produces the desired *o*-benzylbenzaldehyde and the TDG, which goes on to participate in the next catalytic cycle. A hydroxyl group on the TDG presumably coordinates to the metal center, which may enhance the rate of oxidative addition of Pd(II)-intermediate **B** and make the reaction more practical than the reaction with –OH-absent TDGs. Moreover, the dramatic effect of the counterion (X = TFA vs OAc) on Pd(II) was presumably caused by the basicity of acetate and trifluoroacetate. The basic acetate ion was prone to deprotonate the –OH of the amino alcohol to generate intermediate **C**, inhibiting the catalytic cycle, but the less basic trifluoroacetate favors the formation of **B**, leading to reduced



reaction times and superior yields.

Scheme 4. Proposed Reaction Mechanism

Based on the results of sp^3 C–H arylation, a cascade reaction of the Pd-catalyzed *o*-benzylbenzaldehyde formation and Lewis acid-mediated electrophilic aromatic cyclization (Friedel-Crafts cyclization) was studied. Based on our screening of various Lewis acids, the silver triflate (AgOTf) oxidant was found to produce substituted anthracenes in a one-pot reaction. Although the efficiency of silver triflate for sp^3 C–H arylations is much lower than that of silver trifluoroacetate (*i.e.*, the best silver oxidant for the present system), silver triflate was the sole reagent performing the cyclization step following the sp^3 C–H arylation. Once again, by simply changing the silver salt from AgTFA to AgOTf, the one-pot synthesis of anthracene derivatives was successively achieved in the present $Pd(TFA)_2$-**2c** system (Scheme 5). In addition, the addition of 4-nitroaniline enhances the reactivity and reproducibility of the reaction. Under the newly developed one-pot reaction conditions, the substrate scope was then examined with a special focus on functional group tolerance. This cyclization to generate anthracene derivatives was significantly affected by both electronic and steric environments. Iodobenzenes or tolualdehydes bearing electron-withdrawing substituents showed very poor conversion in the synthesis of anthracenes. Thus, a variety of methyl-substituted and fluoro-substituted anthracenes were synthesized from methyl-substituted iodobenzene and tolualdehyde derivatives. In general, <50% of sp^3 C-H arylated product was cyclized to the corresponding anthracene derivative.



Scheme 5. One-pot synthesis of anthracenes by Pd-catalyzed sp^3 C-H arylations

3. Conclusion

In summary, we have reported an efficient palladium-catalyzed sp^3 C–H bond arylation using amino acid-amino alcohol-type transient directing groups with a silver oxidant. The reaction was efficiently carried out with a wide range of substrates in short reaction times. By simply changing the silver salt to AgOTf, the sp^3-arylated compound is then cyclized. Therefore, various anthracene derivatives can be successfully synthesized by a one-pot reaction using the present reaction conditions.

4. Experimental section

4.1. General Methods.

Concentration of solution was carried out by using a rotary evaporator with a water aspirator, and generally followed by removal of residual solvents on a vacuum line held at 0.1–1 torr. Unless otherwise stated, all commercial reagents and solvents were used without additional purification. All chemicals were purchased from Sigma-Aldrich, TCI, Alfa Aesar chemical company. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates. Visualization on TLC was achieved by the use of UV light (254 nm). Flash column chromatography was undertaken on silica gel (400-630 mesh). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on FT AM 400 or 500 (400 or 500 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak. The following abbreviations were used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Coupling constants, J, were reported in Hertz unit (Hz). Carbon 13 nuclear magnetic resonance spectroscopy (^{13}C NMR) was recorded on FT AM 400 or 500 (100 or 125 MHz) and was fully decoupled by broad band decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.0 ppm of chloroform-d. or 39.5 ppm of DMSO-d_6.

*4.2. Preparation of Oxazoline-based TDG **1***

N-Cbz-L-valine **3a** (2.0 mmol, 503 mg) was reacted with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT, 2.2 mmol, 386 mg) and 4-methylmorpholine (NMM, 6.0 mmol, 0.66 mL) in THF 5 mL at room temperature for 1 h. To mixture solution was added *DL*-phenylglycinol **4a** (2.0 mmol, 274 mg) in THF 5 mL and the mixture was stirred at room temperature for 12 h. The mixture was extracted with ethyl acetate (25 mL) and organic layer was dried with $MgSO_4$, filtered and evaporated. Purification by silica gel column chromatography afforded the corresponding amide **5a**.

5a (1.0 mmol, 370 mg) was reacted with *p*-toluenesulfonylchloride (1.1mmol, 210 mg), trimethylamine (3.0mmol, 0.42 mL) and 4-dimethylaminopyridine (0.10 mmol, 12 mg) in DCM 20 mL at room temperature for 24 h. The mixture was extracted with DCM (25 mL) and organic layer was dried with $MgSO_4$, filtered and evaporated. Purification by silica gel column chromatography afforded the corresponding Cbz-protected oxazoline **6**.

6 (0.17 mmol, 60 mg) was stirred under hydrogen atmosphere (1 atm) in the presence of 10% Pd/C (6.0 mg) in MeOH (5 mL) at room temperature for 1 h. After filtering the mixture through celite followed by evaporation of the volatile materials in vacuo. Purification by silica gel column chromatography afforded the corresponding oxazoline-based TDG **1**.

.

*4.3. Typical Procedure for the Preparation of Amino Alcohol-based TDGs **2a–2e***

N-Cbz-protected amino acid **3a**, **3b** or **3c** (2 mmol) was reacted with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT, 2.2 mmol, 386 mg) and 4-methylmorpholine (NMM, 6 mmol, 0.66 mL) in THF 5 mL at room temperature for 1 h. To mixture solution was added amino alcohol **4a**, **4b** or **4c** (2 mmol) in THF 5 mL and the mixture was stirred at room temperature for 12 h. The mixture was extracted with ethyl acetate (25 mL) and

organic layer was dried with $MgSO_4$, filtered and evaporated. Purification by silica gel column chromatography afforded the corresponding amide **5a**–**5e**.

The amide **5a**–**5e** was stirred under hydrogen atmosphere (1 atm) in the presence of 10% Pd/C (6 mg) in MeOH (10 mL) at room temperature for 2 h. After filtering the mixture through celite followed by evaporation of the volatile materials in vacuo. Purification by silica gel column chromatography afforeded the corresponding TDGs **2a**–**2e**.

*4.4. Typical Procedure for the Pd-Catalyzed sp^3 C–H Arylation **9a–9u***

o-Tolualdehyde (0.24 mmol), iodobenzene (0.2 mmol), silver trifluoroacetate (0.3 mmol, 66 mg), palladium trifluoroacetate (0.02 mmol, 7 mg), Phe-Me_2 ligand (0.08 mmol, 19 mg), acetic acid (1.8 mL) and H_2O (0.2 mL) were added to a vial. The mixture was heated to 90 ^oC for 12 h. The reaction mixture was allowed to cool to room temperature and filtered through a silica gel pad, concentrated in vacuum. The desired product was isolated by a silica gel column chromatography or preparative TLC.

*4.5. Typical Procedure for the Preparation of Anthracenes **10a–10f***

o-Tolualdehyde (0.24 mmol), iodobenzene (0.2 mmol), silver trifluoromethanesulfonate (0.3 mmol, 77 mg), Phe-Me_2 ligand (0.08 mmol, 19 mg), 4-nitroaniline (0.4 mmol, 55 mg), palladium trifluoroacetate (0.02 mmol, 7 mg), acetic acid (1.8 mL) and H_2O (0.2 mL) were added to a vial. The mixture was heated to 120 ^oC for 24 h. The reaction mixture was allowed to cool to room temperature and filtered through a silica gel pad, concentrated in vacuum. The desired product was isolated by a silica gel column chromatography or preparative TLC.

4.6. The Characterization data of products

*4.6.1. Benzyl ((S)-1-(((R, or S)-2-hydroxy-1-phenylethyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (**5a**)*[23]

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.36-8.34 (d, 1H, *J* = 8.1 Hz, 5a(S,S)), 8.23-8.21(d, 1H, *J* = 8.1 Hz, **5a**(S,R)), 7.37-7.22 (m, 11H, , **5a**(S,S) + **5a**(S,R)), 5.05 (s, 1H, , **5a**(S,S)), 5.02(s, 1H, **5a**(S,R)), 4.86-4.83 (m, 2H, , **5a**(S,S) + **5a**(S,R)), 3.98-3.90 (m, 1H, , **5a**(S,S) + **5a**(S,R)), 3.57-3.54 (m, 2H, , **5a**(S,S) + **5a**(S,R)), 2.00-1.92 (m, 1H, **5a**(S,S) + **5a**(S,R)), 0.89-0.84 (m, 6H, **5a**(S,R)), 0.80-0.76 (m, 6H, **5a**(S,S)); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.3, 156.6, 141.7, 141.5, 137.6, 128.8, 128.5, 128.4, 128.2, 128.1, 128.1, 127.5, 127.4, 127.2, 65.8, 65.1, 60.8, 60.6, 55.44, 55.38, 31.1, 30.8, 19.75, 19.69, 18.7, 18.5.

*4.6.2. (S)-Benzyl (1-((1-hydroxy-2-methylpropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (**5b**)*

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.36-7.30 (m, 6H), 7.17-7.15 (d, 1H, *J* = 8.8 Hz), 5.03 (s, 2H), 4.85-4.82 (t, 1H, *J* = 5.5 Hz), 3.84-3.80 (t, 1H, *J* = 7.9 Hz), 3.40-3.34 (m, 3H) 1.92-1.87 (m, 1H), 1.17 (s, 6H), 0.86-0.81 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.0, 156.1, 137.2, 128.3, 127.8, 127.6, 67.6, 65.3, 60.4, 54.4, 40.1, 40.0, 39.7, 39.5, 39.3, 39.1, 38.9, 30.6, 23.5, 23.3, 19.2, 18.1; ESI-MS(+) m/z calcd. For $C_{17}H_{27}N_2O_4$ $[M+H]^+$: 323.1965, found $[M+H]^+$: 323.1965.

*4.6.3. (S)-Benzyl (1-((1-hydroxy-2-methylpropan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**5c**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.19 (m, 11H), 5.66 (br s, 1H), 5.45 (br s, 1H), 5.08 (s, 2H), 4.29-4.28 (br d, 1H), 3.50-3.43 (m, 2H), 3.13-3.09 (dd, 1H, *J* = 13.5 Hz, *J* = 6.1 Hz), 2.97-2.93 (dd, 1H, *J* = 13.5 Hz, *J* = 8.3 Hz), 1.11 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 171.2, 156.0, 136.3, 136.0, 129.3, 128.7, 128.5, 128.2, 128.0, 127.1, 69.3, 67.0, 56.8, 56.0, 38.9, 24.3, 23.9; ESI-MS(+) m/z calcd. For $C_{21}H_{27}N_2O_4$ $[M+H]^+$: 371.1965, found $[M+H]^+$: 371.1965.

*4.6.4. (S)-Benzyl (1-((1-hydroxy-2-methylpropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (**5d**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.34 (m, 5H), 6.10 (br s, 1H), 5.18-5.10 (m, 3H), 4.08-4.02 (m, 1H), 3.62-3.51 (m, 2H,), 1.69-1.58 (m, 2H, 1.51-1.47 (m, 1H), 1.27-1.24 (d, 6H, *J* = 10.9 Hz), 0.92-0.94 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 156.4, 136.0, 128.6, 128.3, 128.1, 69.8, 67.2, 56.2, 54.1, 41.1, 24.7, 24.6, 24.3, 22.9, 22.0; ESI-MS(+) m/z calcd. For $C_{18}H_{29}N_2O_4$ $[M+H]^+$: 337.2122, found $[M+H]^+$: 337.2122.

*4.6.5. (S)-Benzyl (1-(tert-butylamino)-1-oxo-3-phenylpropan-2-yl)carbamate (**5e**)*[24]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.14 (m, 10H), 5.42 (br s, 1H), 5.08-5.02 (m, 3H), 4.15 (br s, 1H), 3.08-3.04 (dd, 1H, J = 12.8 Hz, *J* = 5.3 Hz), 2.81-2.79 (m, 1H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 155.8, 136.8, 136.2, 129.4, 128.7, 128.5, 128.1, 128.0, 127.0, 66.9, 56.8, 51.3, 39.3, 28.4.

*4.6.6. Benzyl ((1S)-2-methyl-1-((R or S)-4-phenyl-4,5-dihydrooxazol-2-yl)propyl)carbamate (**6**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.21 (m, 10H, **6**(S,S) + **6**(S,R)), 6.03-5.87 (d, 2H, *J* = 9.0 Hz, **6**(S,S) + **6**(S,R)), 5.18-5.08 (m, 3H, **6**(S,S) + **6**(S,R)), 4.65-4.59 (m, 1H, **6**(S,S) + **6**(S,R)), 4.56-4.48 (m, 1H, **6**(S,S) + **6**(S,R)), 4.12-4.02 (m, 1H, **6**(S,S) + **6**(S,R)), 2.24-2.16 (m, 1H, **6**(S,S) + **6**(S,R) + **6**(S,S) + **6**(S,R)), 1.04-1.02 (d, 3H, *J* = 6.6 Hz, **6**(S,S) + **6**(S,R)), 0.96-0.95 (d, 3H, *J* = 6.8 Hz, **6**(S,S) + **6**(S,R)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.78, 167.61, 158.1, 141.7, 141.6, 136.3, 128.6, 128.6, 128.3, 127.94, 127.91, 127.53, 127.50, 126.50, 126.46, 69.11, 69.07, 66.7, 54.5, 54.4, 31.4, 29.6, 18.84, 18.78, 17.5; ESI-MS(+) m/z calcd. For $C_{21}H_{25}N_2O_3$ $[M+H]^+$: 353.1860, found $[M+H]^+$: 353.1860.

*4.6.7. (S)-2-Methyl-1-((R or S)-4-phenyl-4,5-dihydrooxazol-2-yl)propan-1-amine (**1**)*[25].

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.24 (m, 5H, **1**(S,S)+**1**(S,R)), 5.22-5.18 (m, 1H, **1**(S,S)+**1**(S,R)), 5.22-5.18 (t, 1H, *J* = 9.9 Hz, **1**(S,S)+**1**(S,R)), 4.69-4.65, (dd, 1H, *J* = 8.5 Hz, *J* = 10.2 Hz, **1**(S,S)), 4.68-4.63 (dd, 1H, *J* = 8.5 Hz, *J* = 10.3 Hz, **1**(S,R)), 4.15-4.11 (t, 1H, *J* = 8.4 Hz, **1**(S,R)), 4.14-4.10 (t,

1H, *J* = 8.5 Hz, **1**(S,S)), 3.48-3.45 (dd, 1H, *J* = 5.4 Hz, *J* = 1.2 Hz, **1**(S,S)+**1**(S,R)), 2.12-2.10. (m, 1H, **1**(S,S)+**1**(S,R)), 1.051-1.034(d, 3H, *J* = 6.8 Hz, **1**(S,S)), 1.044-1.027 (d, 3H, *J* = 6.8 Hz, 1(S,R)), 1.017-1.000 (d, 3H, *J* = 6.8 Hz, **1**(S,S)), 1.012-0.995 (d, 3H, *J* = 6.8 Hz, **1**(S,R)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 170.8, 142.01, 141.97, 128.56, 128.54, 127.40, 127.38, 126.44, 126.40, 74.8, 74.7, 69.13, 69.06, 55.4, 55.3, 32.1, 32.0, 19.3, 17.5, 17.3.

*4.6.8. (S)-2-Amino-N-((R or S)-2-hydroxy-1-phenylethyl)-3-methylbutanamide (**2a**)*[25, 26]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16-8.14 (d, 1H, *J* = 7.4 Hz, **2a**(S,S)), 8.09-8.08 (d, 1H, *J* = 7.2 Hz, **2a**(S,R)) 7.37-7.28 (m, 5H, **2a**(S,S)+**2a**(S,R)), 5.10-5.04 (m, 1H, **2a**(S,S)+**2a**(S,R)), 3.87-3.83 (m, 2H, **2a**(S,S)+**2a**(S,R)), 3.41-3.40 (d, 1H, *J* = 4.6 Hz, **2a**(S,S)) , 3.32-3.31 (d, 1H, *J* = 3.9 Hz, **2a**(S,R)), 2.86 (br s, 3H, **2a**(S,S)+**2a**(S,R)), 2.33-2.21 (m, 1H, **2a**(S,S)+**2a**(S,R)), 0.98-0.96 (dd, 6H, *J* = 6.9 Hz, *J* = 1.4 Hz, **2a**(S,S)), 0.91-0.90 (d, 3H, *J* = 6.9 Hz, **2a**(S,R)), 0.79-0.78(d, 3H, *J* = 6.9 Hz, 2a(S,R)); ^{13}C NMR (100 MHz, $CDCl_3$): δ175.1, 174.1, 139.0, 138.8, 128.8, 127.80, 127.77, 126.74, 126.67, 67.0, 66.8, 60.1, 60.0, 56.2, 56.0, 31.0, 30.8, 19.7, 19.4, 16.6, 16.1.

*4.6.9. (S)-2-Amino-N-(1-hydroxy-2-methylpropan-2-yl)-3-methylbutanamide (**2b**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 3.62-3.51 (m, 2H), 3.29-3.28 (d, 1H, *J* = 4.1 Hz), 2.33-2.25 (m, 1H), 1.29-1.28 (d, 6H, *J* = 3.2 Hz), 1.00-0.98 (d, 3H, *J* = 7.0 Hz), 0.85-0.83 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 59.8, 55.8, 30.6, 24.8, 24.6, 19.5, 16.1; ESI-MS(+) m/z calcd. For $C_9H_{21}N_2O_2$ $[M+H]^+$: 189.1598, found $[M+H]^+$: 189.1598.

*4.6.10. (S)-2-Amino-N-(1-hydroxy-2-methylpropan-2-yl)-3-phenylpropanamide (**2c**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (br s, 1H), 7.33-7.22 (m, 5H), 3.68-3.65 (dd, 1H, *J* = 8.4 Hz, *J* = 4.9 Hz), 3.63-3.61 (d, 1H, *J* =12 Hz), 3.52-3.50 (d, 1H, *J* = 12 Hz), 3.20-3.16 (dd, 1H, *J* =13.7 Hz, *J* = 4.9 Hz), 2.85-2.81 (dd, 1H, *J* = 13.7 Hz, *J* = 8.4 Hz), 1.25 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2, 137.1, 129.4, 128.7, 127.0, 70.4, 56.1, 55.7, 40.4, 24.8, 24.4; ESI-MS(+) m/z calcd. For $C_{13}H_{21}N_2O_2$ $[M+H]^+$: 237.1598, found $[M+H]^+$: 237.1598.

*4.6.11. (S)-2-Amino-N-(1-hydroxy-2-methylpropan-2-yl)-4-methylpentanamide (**2d**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H), 3.62-3.51 (m, 2H), 3.41-3.37 (m, 1H), 3.11 (br s, 2H), 1.70-1.66 (m, 2H,), 1.36-1.26 (m, 7H), 0.96-0.91 (dd, 6H, *J* = 12.5 Hz, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 70.6, 55.6, 53.3, 43.6, 24.84, 24.78, 24.6, 23.3, 21.3; ESI-MS(+) m/z calcd. For $C_{10}H_{23}N_2O_2$ $[M+H]^+$: 203.1754, found $[M+H]^+$: 203.1754.

*4.6.12. (S)-2-Amino-N-(tert-butyl)-3-phenylpropanamide (**2e**)*[27]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.24 (m, 5H), 7.00 (br s, 1H), 3.57-3.53 (dd, 1H, *J* = 8.7 Hz, *J* = 4.7 Hz), 3.25-3.20 (dd, 1H, *J* = 13.7 Hz, *J* = 4.7 Hz), 2.81-2.75 (dd, 1H, *J* = 13.7 Hz, *J* = 8.7 Hz), 2.02 (br s, 2H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 137.9, 129.4, 128.6, 126.7, 56.8, 50.5, 40.8, 28.6.

*4.6.13. 2-(4-Hydroxybenzyl)benzaldehyde (**9a**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.24 (s, 1H), 7.87-7.85 (dd, 1H, *J* = 7.6 Hz, 1.4 Hz), 7.55-7.51 (td, 1H, *J* = 7.5 Hz, 1.5 Hz), 7.43-7.39 (td, 1H, *J* = 7.5 Hz, 0.9 Hz), 7.28-7.26 (d, 1H, *J* = 7.4 Hz), 7.00-6.98 (d, 2H, *J* = 8.7 Hz), 6.75-6.73 (d, 2H, *J* = 8.6 Hz), 4.36 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9, 154.1, 143.6, 134.1, 133.7, 132.3, 132.0, 131.5, 129.8, 126.9, 115.4, 37.2.

4.6.14. *2-Benzylbenzaldehyde (**9b**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.26 (s, 1H), 7.85-7.87 (dd, 1H, *J* = 7.6 Hz, 1.4 Hz), 7.55-7.51 (td, 1H, *J* = 7.5 Hz, 1.5 Hz), 7.44-7.42 (td, 1H, *J* = 7.6 Hz, 1.0 Hz), 7.30-7.26 (m, 3H), 7.21-7.14 (m, 3H), 4.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 143.0, 140.2, 133.9, 132.0, 131.6, 128.8, 128.6, 127.0, 126.3, 38.0.

4.6.15. *2-(3-Methylbenzyl)benzaldehyde (**9c**)*[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.27 (s, 1H), 7.89-7.86 (dd, 1H, *J* = 7.6 Hz, 1.5 Hz), 7.55-7.51 (td, 1H, *J* = 7.5 Hz, 1.5 Hz), 7.44-7.40 (td, 1H, *J* = 7.4 Hz, 0.9 Hz), 7.28-7.26 (d, 1H, *J* = 7.7 Hz), 7.19-7.15 (t, 1H, *J* = 7.6 Hz), 7.03-7.00 (d, 1 H, *J* = 7.6 Hz), 6.97-6.93 (m, 2H), 4.42 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 143.1, 140.2, 138.2, 133.9, 131.7, 131.6, 129.5, 128.4, 127.0, 126.9, 125.8, 37.9, 21.4.

*4.6.16. 2-(4-Methylbenzyl)benzaldehyde (**9d**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.26 (s, 1H), 7.87-7.85 (dd, 1H, *J* = 7.6 Hz, 1.4 Hz), 7.54-7.50 (td, 1H, *J* = 7.5 Hz, 1.4 Hz), 7.42-7.38 (td, 1H, *J* = 7.5 Hz, 0.7 Hz), 7.27-7.25 (d, 1H, *J* = 7.4 Hz), 7.09-7.07 (d, 2H, *J* = 7.9 Hz), 7.03-7.02 (d, 2H, *J* = 8.0 Hz), 4.40 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 143.4, 137.2, 135.8, 133.9, 131.8, 131.6, 129.3, 128.7, 126.9, 37.6, 21.0.

*4.6.17. 2-(2-Methoxybenzyl)benzaldehyde (**9e**)*[28]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.36 (s, 1H), 7.90-7.87 (dd, 1H, *J* = 7.7 Hz, 1.4 Hz), 7.49-7.47 (td, 1H, *J* = 7.5 Hz, 1.6 Hz), 7.39-7.35 (td, 1H, *J* = 7.5 Hz, 0.6 Hz), 7.24-7.19 (m, 2H), 6.95-6.93 (dd, 1H, J = 7.3 Hz), 6.88-6.84 (m, 2H), 4.40 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 157.0, 143.3, 134.0, 133.8, 131.3, 130.2, 130.0, 128.7, 127.7, 126.6, 120.6, 110.3, 55.2, 31.8.

*4.6.18. 2-(4-Methoxybenzyl)benzaldehyde (**9f**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.26 (s, 1H), 7.87-7.85 (dd, 1H, *J* = 7.6 Hz, 1.4 Hz), 7.54-7.50

(td, 1H, *J* = 7.5 Hz, 1.5 Hz), 7.43-7.39 (td, 1H, *J* = 7.6 Hz, 0.9 Hz), 7.27-7.25 (d, 1H, *J* = 7.6 Hz), 7.07-7.05 (d, 2H, *J* = 8.8 Hz), 6.83-6.81 (d, 2H, *J* = 8.8 Hz), 4.39 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 158.0, 133.9, 132.3, 131.9, 131.5, 129.7, 126.9, 113.9, 55.2, 37.1.

*4.6.19. 2-(4-Acetylbenzyl)benzaldehyde (**9g**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.17 (s, 1H), 7.88-7.84 (m, 3H), 7.57-7.53 (td, 1H, *J* = 7.5 Hz, 1.6 Hz), 7.48-7.34 (td, 1H, *J* = 7.5 Hz, 1.2 Hz), 7.27-7.22 (m, 3H), 4.51 (s, 2H), 2.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 192.5, 145.9, 141.6, 135.3, 134.0, 133.9, 133.5, 131.8, 128.9, 128.6, 127.3, 38.2, 26.5; ESI-MS(+) m/z calcd. For $C_{16}H_{14}NaO_2$ $[M+Na]^+$: 261.0886, found $[M+Na]^+$: 261.0891.

*4.6.20. 3-(2-Formylbenzyl)benzoic acid (**9h**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20, (s, 1H), 7.95-7.85 (m, 3H), 7.58-7.54(td, 1H, J = 7.5 Hz, 1.5 Hz), 7.48-7.44(td, 1H, *J* = 7.5 Hz, 1.2 Hz), 7.42-7.36(m, 2H), 7.29-7.7.26(d, 1H, *J* = 7.6 Hz), 4.52 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.6, 171.0, 142.0, 140.8, 134.3, 134.0, 133.8, 133.4, 131.7, 130.4, 129.4, 128.7, 128.2, 127.3, 37.9.

*4.6.21. 4-(2-Formylbenzyl)benzoic acid (**9i**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.18, (s, 1H), 8.02-8.00 (d, 2H, *J* = 8.4 Hz), 7.87-7.85(dd, 1H, *J* = 7.6 Hz, 1.5 Hz), 7.58-7.54 (td, 1H, *J* = 7.5 Hz, 1.6 Hz), 7.49-7.45(td, 1H, *J* = 7.5 Hz, 1.2 Hz), 7.28-7.7.24(m, 3H), 4.53 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.6, 171.0, 146.7, 141.6, 134.0, 133.9, 133.5, 131.8, 130.5, 128.9, 127.4, 127.2, 38.3.

*4.6.22. Methyl 3-(2-formylbenzyl)benzoate (**9j**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 7.88-7.84 (m, 3H), 7.56-7.52 (td, 1H, *J* = 7.5 Hz,1.6 Hz), 7.60-7.44 (td, 1H, *J* = 7.5 Hz, 1.2 Hz), 7.35-7.33 (m, 2H), 7.27-7.25 (d, 1H, J = 7.6 Hz), 4.50 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 167.0, 142.1, 140.6, 134.0, 133.8, 133.4, 133.1, 131.7, 130.4, 129.8, 128.6, 127.6, 127.2, 52.1, 37.9.

*4.6.23. Methyl 4-(2-formylbenzyl)benzoate (**9k**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.18 (s, 1H), 7.95-7.92 (d, 2H, *J* = 8.5 Hz), 7.86-7.84 (dd, 1H, *J* = 7.6 Hz, 1.5 Hz), 7.56-7.52 (td, 1H, *J* = 7.5 Hz, 1.6 Hz), 7.47-7.43 (td, 1H, *J* = 7.5 Hz, 1.2 Hz), 7.26-7.24 (d, 1H, *J* = 7.5 Hz), 7.22-7.20 (d, 2H, *J* = 8.6 Hz), 4.50 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 166.9, 145.7, 141.7, 133.93, 133.86, 133.3, 131.7, 129.8, 128.8, 128.2, 127.3, 52.0, 38.2.

*4.6.24. 2-(3-Fluorobenzyl)benzaldehyde (**9l**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 7.87-7.85 (dd, 1H, *J* = 7.6 Hz, 1.4 Hz), 7.57-7.53 (td, 1H, *J* = 7.5 Hz, 1.5), 7.47-7.43 (td, 1H, *J* = 7.5 Hz, 1.1 Hz), 7.27-7.21 (m, 2H), 6.95-6.81 (m, 3H), 4.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 164.2, 161.7, 142.85, 142.78, 142.0, 134.0, 133.0, 131.7, 129.9, 129.8, 127.3, 124.43, 124.41, 115.8, 115.5, 113.3,113.1, 37.83, 37.82.

*4.6.25. 2-(4-Fluorobenzyl)benzaldehyde (**9m**)*[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.21 (s, 1H), 7.87-7.84 (dd, 1H, *J* = 7.6 Hz, 1.4 Hz), 7.56-7.52 (td, 1H, *J* = 7.5 Hz, 1.5 Hz), 7.45-7.42 (td, 1H, *J* = 7.5 Hz, 1.0 Hz), 7.26-7.24 (d, 1H, *J* = 7.7 Hz), 7.12-7.09 (m, 2H), 6.98-6.93 (m, 2H), 4.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 162.6, 160.2, 133.9, 132.8, 131.5, 130.2, 130.1, 127.1, 115.4, 115.2, 37.3.

*4.6.26. 2-(4-Chlorobenzyl)benzaldehyde (**9n**)*[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.19 (s, 1H), 7.86-7.84 (dd, 1H, *J* = 7.6 Hz, 1.5 Hz), 7.56-7.52 (td, 1H, *J* = 7.5 Hz, 1.5 Hz), 7.46-7.42 (td, 1H, *J* = 7.5 Hz, 1.1 Hz), 7.26-7.22 (m, 3H), 7.09-7.07 (d, 2H, *J* = 8.6 Hz), 4.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 142.3, 138.7, 133.9, 133.8, 133.1, 132.0, 131.6, 130.1, 128.6, 127.2, 37.5

*4.6.27. 2-(3-Nitrobenzyl)benzaldehyde (**9o**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.05-8.03 (d, 1H, *J* = 8.1 Hz), 7.99 (s, 1H), 7.87-7.85 (dd, 1H, *J* = 7.5 Hz, 1.4 Hz), 7.61-7.57 (td, 1H, *J* = 7.5 Hz, 1.5 Hz), 7.53-7.49 (m, 2H), 7.45-7.41 (t, H, *J* = 7.9 Hz), 7.31-7.29 (d, 1H, *J* = 7.5 Hz), 4.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 148.3, 142.4, 140.7, 135.1, 134.7, 134.1, 133.8, 131.9, 129.2, 127.7, 123.5, 121.4, 38.0.

*4.6.28. 2-(4-Nitrobenzyl)benzaldehyde (**9p**)*[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.11 (s, 1H), 8.13-8.11 (m, 2H), 7.87-7.85 (dd, 1H, *J* = 7.5 Hz, 1.5 Hz), 7.61-7.57 (td, 1H, *J* = 7.5 Hz, 1.5 Hz), 7.53-7.49 (td, 1H, *J* = 7.5 Hz, 1.3 Hz), 7.32-7.28 (m, 3H), 4.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 148.1, 146.4, 140.5, 134.7, 134.0, 133.8, 131.9, 129.5, 127.7, 123.6, 38.3.

*4.6.29. 5-Methyl-2-(3-nitrobenzyl)benzaldehyde (**9q**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (s, 1H), 8.04-8.02 (m, 1H), 7.97 (s, 1H), 7.65 (s, 1H), 7.52-7.50 (d, 1H, *J* = 7.6 Hz), 7.44-7.38 (m, 2H), 7.20-7.18 (d, 1H, *J* = 7.7 Hz), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9, 148.3, 142.7, 137.7, 137.5, 135.2, 135.0, 134.8, 133.6, 131.9, 129.2, 123.4, 121.3, 37.6, 20.8.

*4.6.30. 4-Methyl-2-(3-nitrobenzyl)benzaldehyde (**9r**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.05-8.03 (m, 1H), 7.99 (s, 1H), 7.75-7.73 (d, 1H, *J* = 7.7 Hz), 7.53-7.51 (m, 1H), 7.45-7.41 (t, 1H, *J* = 7.9 Hz), 7.31-7.26 (d, 1H, *J* = 7.8 Hz), 7.10 (s, 1H), 4.51(s, 2H), 2.42(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 148.3, 145.2, 142.5, 140.6, 135.11, 135.07, 132.7, 131.5, 129.2, 128.3., 123.4, 121.3, 38.0, 21.8.

*4.6.31. 3-Methyl-2-(3-nitrobenzyl)benzaldehyde (**9s**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.04-8.01 (m, 1H), 7.85 (s, 1H), 7.76-7.74 (dd, 1H, *J* = 7.4 Hz, *J* = 1.4 Hz), 7.51-7.35 (m, 4H), 4.62 (s, 2H), 2.31(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 148.3, 134.8, 139.0, 138.2, 136.3, 134.5, 134.3, 132.7, 129.2, 127.6, 122.8, 121.2, 33.3, 19.6.

*4.6.32. 5-Fluoro-2-(3-nitrobenzyl)benzaldehyde (**9t**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.10 (d, 1H, *J* = 1.0 Hz), 8.07-8.04 (m, 1H), 7.97 (s, 1H), 7.57-7.54 (td, 1H, *J* = 8.5 Hz, *J* = 1.7 Hz), 7.50-7.43 (m, 2H), 7.30-7.29 (dd, 1H, *J* = 6.6 Hz, *J* = 1.7 Hz), 4.5 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 190.9, 163.1, 160.6, 148.4, 142.1, 136.52, 136.49, 135.3, 135.2, 134.9, 133.7, 133.6, 129.4, 123.4, 121.6, 121.3, 121.1, 120.0, 119.7, 37.2.

*4.6.33. 4-Fluoro-2-(3-nitrobenzyl)benzaldehyde (**9u**)*[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (s, 1H), 8.08-8.70 (d, 1H, *J* = 8.0 Hz), 8.00 (s, 1H), 7.90-7.87 (dd, 1H, *J* = 8.6 Hz, J = 5.9 Hz), 7.53-7.45 (m, 2H), 7.20-7.15 (td, 1H, *J* = 8.1 Hz, *J* = 2.5 Hz), 6.97-6.94 (dd, 1H, *J* = 9.4 Hz, *J* = 2.4 Hz), 4.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 167.0, 164.4, 148.4, 144.34, 144.25, 131.4, 137.5, 137.4, 135.1, 130.40, 130.37, 129.5, 123.6, 121.7, 119.0, 118.8, 114.8, 114.6, 37.8.

*4.6.34. Anthracene (**10a**)*[29]

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 2H), 8.00-8.03 (m, 4H), 7.49-7.46 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 131.7, 128.1, 126.2, 125.3.

*4.6.35. 2-Methylanthracene (**10b**)*[30]

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.32 (s, 1H), 7.98-8.00 (m, 2H), 7.91-7.93(d, 1H, *J* = 8.7 Hz), 7.76 (s, 1H), 7.43-7.45 (m, 2H), 7.30-7.32 (dd, 2H, *J* = 8.7 Hz, *J* = 1.6 Hz), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.9, 132.0, 131.8, 131.2, 130.3, 128.24, 128.16, 128.0, 127.9, 126.3, 125.9, 125.2, 125.1, 124.9, 22.0.

*4.6.36. 1,3-Dimethylanthracene (**10c**)*[30]

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.32 (s, 1H), 8.04-8.02 (m, 1H), 7.99-7.97 (m, 1H), 7.63 (s, 1H), 7.47-7.44 (m, 2H), 7.17 (s, 1H), 2.80 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.6, 134.0, 132.3, 131.6, 131.1, 130.0, 128.6, 128.5, 127.8, 125.7, 125.2, 124.84, 124.81, 122.6, 21.9, 19.6.

*4.6.37. 1-Methylanthracene (**10d**)*[29]*, 2-Methylanthracene (**10b**)*[29]

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (s, 1H, **10d**), 8.43 (s, 1H, **10d**), 8.38 (s, 1H, **10b**), 8.32 (s, 1H, **10b**), 7.98-8.07 (m, 2H, **10d** + **10b**), 7.91-7.93(d, 1H, *J* = 8.7 Hz, **10b**), 7.88-7.89 (d, 1H, *J* = 8.5 Hz, **10d**), 7.76 (s, 1H, **10b**), 7.42-7.49 (m, 2H, **10d** + **10b**), 7.36-7.39(dd, 1H, *J* = 8.5 Hz, *J* = 6.7 Hz, **10d**), 7.30-7.32 (dd, 1H, *J* = 8.7 Hz, *J* = 1.6 Hz, **10b**), 2.83 (s, 3H, **10d**), 2.56 (s, 3H, **10b**); ^{13}C NMR (125 MHz, $CDCl_3$, for 10b): δ 134.9, 132.0, 131.8, 131.2, 130.3, 128.24, 128.16, 128.0, 127.9, 126.3, 125.9, 125.2, 125.1, 124.9, 22.0.

*4.6.38. 2-Fluoroanthracene (**10e**)*[29]*, 1-Fluoroanthracene (**10f**)*[31]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H, **10e**), 8.43 (s, 1H, **10f**), 8.35 (s, 1H, **10f**), 8.07-8.06 (m, 1H, **10e**), 8.02-7.97 (m, 3H, **10f**), 7.80-7.79 (d, 1H, *J* = 8.6 Hz, **10e** + **10f**),7.59-7.57 (dd, 1H, *J* =10.2 Hz, *J* = 2.3 Hz, **10f**), 7.52-7.45 (m, 2H, **10e** + **10f**), 7.40-7.35 (m, 1H, **10e**), 7.30-7.26 (m, 1H, **10f**), 7.14-7.10 (1H, **10e**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 158.9, 132.2, 131.8, 131.7, 131.1, 131.0, 130.9, 129.0, 128.3, 127.7, 126.64, 126.63, 126.0, 125.4, 125.32, 125.25, 117.4, 117.1, 109.8, 109.6.

5. Acknowledgments

This research was supported by the Science Research Center (2016R1A5A1009405) and Basic Science Research Program (2016R1C1B1011076) through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning. K. Yoo was supported by NRF Grant funded by the Korean Government (NRF-2017H1A2A1045495-Fostering Core Leaders of the Future Basic Science Program/Global Ph.D. Fellowship Program).

6. Appendix A. Supplementary data

^{1}H and ^{13}C spectra for all obtained compounds. This material is available free of charge via the Internet at https://

7. References

1. (a) Abdel-Shafy HI, Mansour MSM. *Egypt. J. Pet.* 2016;25:107; (b) Fetzer JC. *Polycyclic Arom. Compd.* 2007;27:143;(c) Bouas-Laurent H, Castellan A, Desvergne J-P, Lapouyard R. *Chem. Soc. Rev.* 2000;29:43; (d) Becker H-D. *Chem. Rev.* 1993; 93:145.

2. (a) Xu J, Niu G, Wei X, Lan M, Zeng L, Kinsella JM, Sheng R. *Dyes Pigments* 2017;139:166; (b) Stanley LH, Anstöter CS, Verlet JRR. *Chem. Sci.* 2017;8:3054; (c) Moon H, Jun YW, Kim D, Ryu HG, Wang T, Kim KH, Huh Y, Jung J, Ahn KH. *Chem. Asian J.* 2016;11:2518; (d) Park H-J, Jung H, Kim S-H, Park M, Kim J-H, Son J, Jung BJ, Hwang D-H, Lee C, Lee J-K, Yoon JG, Yoon SY. *J. Polym. Sci. Part A: Polym. Chem.* 2015;53:1252.

3. (a) Dhangar G, Serrano JL, Schulzke C, Gunturu KC, Kapdi AR. *ACS Omega* 2017;2:3144; (b) Zhou Y, Zhang H-Y, Zhang Z-Y, Liu Y. *J. Am. Chem. Soc.* 2017;139:7168; (c) Sung MJ, Chubachi H, Sato R, Shin M-K, Kwon S-K, Pu Y-J, Kim Y-H. *J. Mater. Chem. C.* 2017;5:1090; (d) Chen M, Zhao Y, Yan L, Yang S, Zhu Y, Murtaza I, He G, Meng H, Huang W. *Angew. Chem., Int. Ed.* 2017;*56*: 722.

4. (a) Li X, Chen D, Liu Y, Yu Z, Xia Q, Xing H, Sun W. *CrystEngComm*, 2016;18:3696; (b) Chen D, Xing H, Su Z, Wang C. *Chem. Commun.* 2016:*52*:2019; (c) Ma S, Sun D, Simmons J M, Collier CD, Yuan D, Zhou H-C. *J. Am. Chem. Soc.* 2008;130:1012.

5. (a) Chanphai P, Agudelo D, Tajmir-Riahi HA, *Journal of Biomolecular Structure and Dynamics* 2017;35:2257; (b) Kellett K, Broome JH, Zloh M, Kirton SB, Fergus S, Gerhard U, Stair JL, Wallace KJ. *Chem. Commun*. 2016;52:7474; (c) Sangthong S, Ha H, Teerawattananon T, NgaMrojanavanich N, Neamati N, Muangsin N. *Bioorg. Med. Chem. Lett.* 2013;23:6156; (d) Corrêa TA, Alves CCS, Castro SBR, Oliveira EE, Franco LS, Ferreira AP, de Almeida MV. *Chem. Biol. Drug. Des.* 2013;82:463.
6. (a) Bradsher CK. *Chem. Rev*. 1946;38:447; (b) Rafiq SM, Sivasakthikumaran R, karunakaran J, Mohanakrishnan AK. *Eur, J. Org. Chem.* 2015;5099; (c) Kuninobu Y, Tatsuzaki T, Matsuki T, Takai K. *J. Org. Chem.* 2011;76:7005; (d) Li G, Zhou S, Su G, Liu Y, Wang PG. *J. Org. Chem.* 2007;72 :9830.
7. (a) Boyarskiy VP, Ryabukhin DS, Bokach NA, Vasilyev AV. *Chem. Rev.* 2016;116:5894; (b) Shu C, Chen C-B, Chen W-X, Ye L-W. *Org. Lett.* 2013;15: 5542.
8. (a) Romero C, Fena D, Pérez D, Guitián E. *Chem. Eur. J.* 2006;12:5677; (b) Yin J, Qu H, Zhang K, Luo J, Zhang X, Chi C, Wu J. *Org. Lett.* 2009;11:3028.
9. (a) Saino N, Kawaji T, Ito T, Matsushita Y, Okamoto S. *Tetrahedron Lett*. 2010;51:1313; (b) Zou Y, Young DD, Cruz-Montanez A, Deiters A. *Org. Lett.* 2008;10:4661; (c) Zhou Y, Porco JA, Snyder JK. *Org. Lett.* 2007;9:393.
10. For selected reviews: (a) Xue X-S, Ji P, Zhou B,Cheng J-P. *Chem. Rev*. 2017;117:8622; (b) Yang Y, Lan J, You J. *Chem. Rev*. 2017;117:8787; (c) Wei Y, Hu P, Zhang M, Su W. *Chem. Rev*. 2017;117:8864; (d) Newton CG, Wang S-G, Oliveira CC, Cramer N. *Chem. Rev*. 2017;117:8908; (e) Shang R, Ilies L, Nakamura E. *Chem. Rev*. 2017;117:9086; (f) Hummel JR, Boerth JA, Ellman JA. *Chem. Rev.* 2017;117: 9163; (g) Park Y, Kim Y, Chang S. *Chem. Rev.* 2017;117:9247; (h) Wencel-Delord J, Glorius F. *Nat. Chem.* 2013;5:369.
11. (a) Qiu Y, Gao S. *Nat. Prod. Rep*. 2016;33:562; (b) Urabe D Asaba T, Inous M. *Chem. Rev.* 2015;115: 9207; (c) Noisier AFM, Brimble MA. *Chem. Rev.* 2014;114:8775; (d) Yamaguchi J, Yamaguchi AD, Itami K. *Angew. Chem., Int. Ed*. 2012;51:8960–; (e) Gutekunst WR, Baran PS. *Chem. Soc. Rev.*, 2011;40: 1976.
12. (a) He J, Wasa M, Chan KSL, Shao Q, Yu J-Q. *Chem. Rev*. 2017;117:8754; (b) Musaev DG, Figg TM, Kaledin AL. *Chem. Soc. Rev*. 2014;43:5009; (c) Balcells D, Clot E, Eisenstein. *Chem. Rev.* 2010;110: 749.
13. (a) Trost BM. *Acc. Chem. Res.* 2002;35:695; (b) Trost BM. *Angew. Chem., Int. Ed.* 1995;34:259; (c) Trost BM. *Science* 1991;254:1471.
14. (a) Kim D-S, Park W-J, Jun C-H. *Chem. Rev*. 2017;117:8977; (b) Park YJ, Park J-W, Jun C-H. *Acc. Chem. Res.* 2008;41:222; (c) Dong Z, Ren Z, Thompson SJ, Xu Y, Dong G. *Chem. Rev*. 2017;117:9333; (d) Huang Z, Lim HN, Mo F, Young MC, Dong G. *Chem. Soc. Rev.* 2015;44:7764.
15. (a) Hu W, Zheng Q, Sun S, Cheng J. *Chem. Commun.* 2017;53:6263; (b) Xu J, Liu Y, Wang Y, Li Y, Xu X, Jin Z. *Org. Lett.* 2017;19:1562; (c) Chen X-Y, Ozturk S, Sorensen EJ. *Org. Lett.* 2017;19:1140; (d) Liu X-H, Park H, Hu J-H, Hu Y, Zhang Q-L, Wang B-L Sun B, Yeung K-S, Zhang F-L, Yu J-Q. *J. Am. Chem. Soc.* 2017;139:888; (e) Piou T, Rovis T. *Nature* 2015;527:86; (f) Wang X-C, Gong W, Fang L-Z, Zhu R-Y, Li S, Engle KM, Yu J-Q. *Nature* 2015;519:334.
16. Zhang F-L, Hong K, Li T-J, Park H, Yu J-Q. *Science* 2016;351:252.
17. (a) He J, Wasa M, Chan KSL, Shao Q, Yu J-Q. *Chem. Rev*. 2017;117:8754; (b) Zhang X, Zheng H, Li J, Xu F, Zhao J, Yan H. *J. Am. Chem. Soc.* 2017;139:14511; (c) Hong K, Park H, Yu J-Q. *ACS Catal*. 2017;7:6938; (d) Zhu R-Y, Liu L-Y, Yu J-Q. *J. Am. Chem. Soc.* 2017;139:12394; (e) Xu Y, Young MC, Dong G. *J. Am. Chem. Soc*. 2017;139:5716; (f) Yada A, Liao W, Sato Y, Murakami M. *Angew. Chem. Int. Ed*. 2017;56:1073; (g) Chu JCK, Rovis T. *Angew. Chem. Int. Ed.* 2017;56: 2; (h) Liu Y, Ge H. *Nat. Chem.* 2017;9:26; (i) Yang K, Li Q, Liu Y, Li G, Ge H. *J. Am. Chem. Soc.* 2016;138:12775; (j) Xu Y, Young MC, Wang C, Magness DM, Dong G. *Angew. Chem., Int. Ed.* 2016;55: 9084.
18. Kamiński ZJ, Paneth P, Rudziński J. *J. Org. Chem.* 1998;63:4248.
19. Ma F, Lei M, Hu L. *Org. Lett.* 2016;18:2708.
20. Xu J, Liu Y, Wang Y, Li Y, Xu X, Jun Z. *Org. Lett.* 2017;19:1562.
21. Lapointe D, Fagnou K. *Chem. Lett.* 2010;39:1118.
22. (a) Sehnal P, Taylor RJK, Failam IJS. *Chem. Rev.* 2010;110:824; (b) Xu KM, Li BJ, Yang Z, Shi Z. *J. Chem. Soc. Rev.* 2010;39:712.
23. Vastila P, Pastor IM, Adolfsson H. *Chem. Eur. J.* 2003;9:4031.
24. Le Bailly BAF, Clayden J. *Chem. Commun.* 2014;50:7949.
25. Vastila P, Pastor IM, Adolfsson H. *J Org. Chem.* 2005;70:2921.
26. Demuynck ALW, Vanderleyden J, Selsa BF. *Adv. Synth. Catal*. 2010;352:2421.
27. Shimizu Y, Noshita M, Mukai Y, Morimoto H, Ohshima T. *Chem. Commun*. 2014;50:12623.
28. Dewkar GK, Peddi S, Mosier PD, Roth BL, Richard B Westkaemper RB. *Bioorg. Med. Chem. Lett*. 2008;18:5268.
29. Fujita T, Takahashi I, Hayashi M, Wang J, Fuchibe K, Ichikawa J. *Eur. J. Org. Chem.* 2017;262.
30. Wang C, Wan J, Zheng Z, Pan Y. *Tetrahedron* 2007;63:5071.
31. Suzuki N, Fujita T, Amsharov KY, Ichikawa J. *Chem. Commun.* 2016;52:12948.