REVIEW

α -C(sp³)-H Arylation of Cyclic Carbonyl Compounds

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Abstract

α -C(sp³)-H arylation is an important type of C-H functionalization. Various biologically significant natural products, chemical intermediates, and drugs have been effectively prepared via C-H functionalization. Cyclic carbonyl compounds comprise of cyclic ketones, enones, lactones, and lactams. The α -C(sp³)-H arylation of these compounds have been exhibited high efficiency in forming C(sp³)-C(sp²) bonds, played a crucial role in organic synthesis, and attracted majority of interests from organic and medicinal communities. This review focused on the most significant advances including methods, mechanism, and applications in total synthesis of natural products in the field of α -C(sp³)-H arylations of cyclic carbonyl compounds in recent years.

Keywords C-H functionalization · α -C(sp³)-H arylation · Cyclic carbonyl compounds

1 Introduction

C-H functionalization is the most powerful method that directly transforms C-H bond to C-R bond (R is any atom except H, such as C, O, N, etc.) (Scheme 1). Since C-H bonds are common in organic compounds, C-H functionalization has an extremely broad space of application. Through direct C-H functionalization, the functionalized substrate [1–7], drug intermediates [8–10], and bioactive natural products with complex structures [11–15] can be successfully synthesized in a highly effective manner. Therefore, it has been regarded as an "eternal theme" in organic chemistry [16, 17]. As an important type of C-H functionalization, the α -C(sp³)-H arylations of cyclic carbonyl compounds (cyclic ketones, enones, lactones and lactams) are affected by ring tension, steric hindrance, and electronic effect, which have been considered to be a tough issue [18, 19]. Considering the important application of the α -C(sp³)-H arylations of

cyclic carbonyl compounds in organic chemistry, medicinal chemistry, and drug development process. Previous reviews summarized the progress in Pd-catalyzed α -C(sp³)-H arylations of carbonyl compounds [20–22], the applications of these reactions in the total synthesis of natural products [23], and the enantioselective approaches [24]. This review mainly focused on the conditions, substrates ranges and the application of α -C(sp³)-H arylation of cyclic carbonyl compounds in recent years.

2 Transition-Metal Catalyzed α -C(sp³)-H Arylation of Cyclic Carbonyl Compounds

2.1 Palladium-Catalyzed α -C(sp³)-H Arylation of Cyclic Carbonyl Compounds

Palladium is the most widely used catalyst in α -C(sp³)-H arylation of cyclic carbonyl compounds, featuring with small amount of catalyst loading and simple operation. The mechanism of well-established Pd-catalyzed α -C(sp³)-H arylation has been proposed as shown in Scheme 2. The generally catalytic cycle comprises of three paths (A–C). Oxidative addition of Pd(0) with ArX (X = Cl, Br, I, and OTf) forms complex **i** (path A). Transmetalation of intermediate **i** with enolates (Li, Na, K, Cs, etc.) provide active enol-palladium complexes **ii** which can isomerize to **iii** (path B) [19, 25].

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C-H functionalization:

$\alpha\text{-C}(\text{sp}^3)\text{-H}$ arylation of cyclic carbonyl compounds:

Scheme 1 C-H functionalization and $\alpha\text{-C}(\text{sp}^3)\text{-H}$ arylation of cyclic carbonyl compounds

The organopalladium intermediate **iii** finally converts to $\alpha\text{-aryl}$ compound through reductive elimination (path C).

2.1.1 Palladium-Catalyzed Intramolecular $\alpha\text{-C}(\text{sp}^3)\text{-H}$ Arylations of Cyclic Carbonyl Compounds

In 1988, Ciufolini et al. reported a Pd-catalyzed intramolecular $\alpha\text{-arylation}$ of 1,3-cyclopentadienone **1**, and suggested that forming the "soft" enolate by NaH could significantly improve the yield of **2** (Scheme 3) [26]. Later, Natsume et al. reported a similar Pd-catalyzed $\alpha\text{-arylation}$ of cyclic ketone (**3a-3f**), and found that bridge rings (**4a-4c**) or spiro rings (**4d-4f**) could be prepared by controlling the lengths of α side chains (Scheme 4) [27]. With the strategy, a gram-scale total synthesis of (-)-huperzine A was achieved by Herzon et al. [28]. To achieve an enantioselective intramolecular arylation of **3d**-based analogue, the coordinated catalyst JosiPhos/Pd(OAc)₂ was established by Sasai et al. [29].

Scheme 2 Proposed mechanism for the Pd-catalyzed $\alpha\text{-C}(\text{sp}^3)\text{-H}$ arylation of cyclic carbonyl compounds [25]

Scheme 3 Intramolecular $\alpha\text{-C}(\text{sp}^3)\text{-H}$ arylation of 1,3-cyclopentadienone **1**

Recently, Tang et al. described an asymmetric intramolecular $\alpha\text{-arylation}$ that provided good to excellent enantioselectivities for a wide range of spirocyclic structures (**5a-5h**) by developing an effective *P*-chiral monophosphorus ligand **L1** (Scheme 5) [30]. The method also enabled the formal syntheses of (-)-cannabispirenes A and B (Scheme 6) [30].

Solé et al. designed nitrogen-containing aryl iodide **8a** as the substrate, and under the catalysis of PdCl₂(PPh₃)₂, the intramolecular $\alpha\text{-arylated}$ product **9a** could be obtained in 92% yields, in which the pivotal active Pd complex **8a'** was confirmed by X-ray (Scheme 7) [31]. Jia et al. creatively combined L-proline with Pd(OAc)₂/P(PPh)₃/K₃PO₄/AcOH catalytic system to efficiently realize the intramolecular enantioselective desymmetric $\alpha\text{-arylations}$ of functionalized cyclohexanones (**10a-10j**). More importantly, this method exhibited well functional groups (FGs) tolerance and well compatibility in protonic solvent. However, the yields and *ee* values dramatically decreased when *N* was protected with acyl groups (Scheme 8) [32]. Later, Lu et al. reported the enantioselective desymmetric $\alpha\text{-arylations}$ of functionalized cyclobutanones through a similar Pd/enamine co-catalytic process (Scheme 9, A) [33]. Recently, Shi et al. represented an enantioselective desymmetric $\alpha\text{-arylation}$ of 1,3-diketones which enabled the total synthesis of (-)-parvifoline

Scheme 4 Intramolecular α -C(sp³)-H arylation of α -bromoaryl substituted cyclic ketone **3a-3f**

Entry	ArBr (R ₁ ,R ₂)	product	Yield (%)	ee (%)	Entry	ArBr (R ₁ ,R ₂)	product	Yield (%)	ee (%)
1	5a (R ₁ =H, R ₂ =6-F)		90	86	5	5e (R ₁ =6'-O Me, R ₂ =6-F)		67	84
2	5b (R ₁ =H, R ₂ =5-O Me)		97	90	6	5f (R ₁ =H,R ₂ = 2-pyridine)		79	82
3	5c (R ₁ = 6'-OMe , R ₂ =H)		98	92	7	5g (R ₁ =H,R ₂ = b-thiophene)		98	58
4	5d (R ₁ =7'- F, R ₂ =H)		89	94	8	5h (R ₁ =H,R ₂ =7 -annulene)		98	90

Scheme 5 Spiro-ketones formed via intramolecular enantioselective α -arylation

(Scheme 9, B) [34]. Zhou groups described enantioselective α -arylations of functionalized cycloketones via dynamic

kinetic resolution of α' -center which led to various bridged ketones (Scheme 9, C) [35].

Scheme 6 Formal syntheses of (-)-cannabispirenones A and B **Scheme 7** Intramolecular α -arylation of functionalized cyclohexanone **8a**

Entry	Substrates (R_1R_2)	Yield (%)	ee (%)	Entry	Substrates (R_1R_2)	Yield (%)	ee (%)
1	10a ($\text{R}_1=\text{H}, \text{R}_2=\text{Bn}$)	11a (91)	97	7	10f ($\text{R}_1=4\text{-CO}_2\text{Me}, \text{R}_2=\text{Bn}$)	11f (92)	95
2	10b ($\text{R}_1=4\text{-OMe}, \text{R}_2=\text{Bn}$)	11b (85)	99	8	10g ($\text{R}_1=4\text{-CO}_2\text{H}, \text{R}_2=\text{Bn}$)	11g (65)	96
3	10c ($\text{R}_1=4\text{-OCF}_3, \text{R}_2=\text{Bn}$)	11c (92)	96	9	10h ($\text{R}_1=3\text{-OMe}, \text{R}_2=\text{Bn}$)	11h (95)	97
4	10d ($\text{R}_1=4\text{-Me}, \text{R}_2=\text{Bn}$)	11d (90)	98	10	10i ($\text{R}_1=3,4\text{-OCH}_2\text{O}, \text{R}_2=\text{Me}$)	11i (94)	99
5	10e ($\text{R}_1=i\text{Pr}, \text{R}_2=\text{Bn}$)	11e (96)	97	11	10j ($\text{R}_1=\text{H}, \text{R}_2=\text{CO}_2\text{Et}$)	11j (39)	70

Scheme 8 Desymmetric enantioselective $\alpha\text{-C}(\text{sp}^3)\text{-H}$ arylations of functionalized cyclohexanones

2.1.2 Palladium-Catalyzed Intermolecular $\alpha\text{-C}(\text{sp}^3)\text{-H}$ Arylations of Cyclic Carbonyl Compounds

Buchwald et al. first reported an intermolecular Pd-catalyzed α -arylation of cyclohexanone **14** with 4-*tert*-butylbromobenzene **15** using $\text{Pd}_2(\text{dba})_3$ (1.5 mol%)/Tol-BINAP (3.6 mol%) to obtain product **16** in 83% yield (Scheme 10) [36]. They speculated that the formation of active enol-palladium-aryl complex in the catalytic cycle was a key step.

This speculation was later supported by the α -arylation of other active enol substrates [37–41].

Subsequently, Buchwald et al. started an asymmetric method for the first time. As a result, 2-methyl-1-benzocyclohexanone **17a** was arylated with aryl bromide **15** under the condition of $\text{Pd}(\text{OAc})_2$ (10–20 mol%)/(s)-(-)-BINAP (12–24 mol%) to give **19a** (yield 73%, 88% ee) [42]. The study also found that under the same catalytic system, 2-methyl-1-benzocyclopentanone **17b** was used

Scheme 9 Desymmetric enantioselective α -C(sp³)-H arylations of functionalized cycloketones **Scheme 10** Intermolecular α -C(sp³)-H arylation of cyclohexanone **14**

as the substrate to react with aryl bromide **18a** leading to the arylated product **19b** with low *ee* value (70%). In view of the fact that these reactions are very sensitive to substrates and aryl bromides, Buchwald et al. screened different substrates and aryl bromides, and finally found that the products (**19c-19e**) with high *ee* value could be obtained by using cyclic ketone **17c** as substrate in cooperation with aryl bromides (**15**, **18a-18b**) (Scheme 11). They also found that the reaction could be carried out under mild conditions (50 °C) using $\text{P}(t\text{Bu})_3$ as the ligand in similar catalytic system [43]. Meanwhile, Hartwig et al. found enantioselective α -arylation of cyclic ketones (**17a-17c**) could be achieved by using phenolic trifluoromethanesulfonate (**20a-20c**) under the condition of $\text{Pd}(\text{dba})_2$ /*(R)*-Difluorophos (Scheme 12). However, ketone **17d** gave the corresponding product with low *ee* value (78%) in this system [44]. Interestingly, nearly comparable yields and *ee* values were obtained by using quinine as the co-catalyst with $\text{Pd}(\text{dba})_2$ [45].

To further evaluate the reaction, Buchwald et al. conducted combinatorial studies on different cyclic ketones (**14** and **21a-21c**), aryl bromides (**15** and **22a-22d**), and phosphine ligands (**L-6** to **L-10**) (Scheme 13). The results showed that the large hindrance biphenyl phosphine ligands combined with $\text{Pd}(\text{OAc})_2$ or $\text{Pd}_2(\text{dba})_3$ exhibiting high catalytic efficiency. It is worth noting that the *ortho*-substituted aryl chloride (**22a**) or *ortho*-disubstituted aryl bromide and aryl bromides containing electron-withdrawing groups (**22b-22d**) exhibited good compatibility to furnish aryl product (**23a-23e**) in 74–96% yields [46]. Similar reports showed that the α -C(sp³)-H arylations of cyclic ketones **17a** and **21a** could also be achieved by using aryl chlorides [20] and azacarbene ligands [47].

With those satisfactory results, Buchwald et al. continued developing such catalytic systems to finally find a new chiral catalytic coordination of phosphine ligand ((*S*)-**L-11** to **L-13**) with $\text{Pd}_2(\text{dba})_3$. Using the system, the asymmetric α -arylations of substrate (**24a-24c**) were carried

Scheme 11 Enantioselective α -C(sp³)-H arylations of cyclic ketones reported by Buchwald et al.

Entry	Substrates	ArBr	Pd mol%	Yields (%)	ee (%)
1			1	19a (73)	88
2			5	19b (79)	70
3			10	19c (86)	95
4			20	19d (80)	94
5			20	19e (75)	98

out at room temperature to form (**26a-26g**) (Scheme 14). Besides 4-methoxybromobenzene **25c**, 4-methyl, 4-tert-butyl, 3-methoxy, and 3-methylbromobenzene (**25a**, **15**, **25b** and **18b**) could give α -arylation products with high yield (72–88%) and high enantioselectivity (80–94% *ee*) [48]. Hartwig et al. reported an asymmetric α -arylations of ketone **27** using aryl bromide **28** (Scheme 15). In the $\text{Pd}_2(\text{dba})_3/(\text{R})$ -difluorophos catalytic system, α -arylation product **30** was obtained with high yield (80%) and excellent enantioselectivity (94% *ee*), and the subsequent total syntheses of (–)-taiwaniaquinone H [49] and (–)-taiwaniaquinol B [50] were completed using **29** as raw materials [51] (Scheme 15).

In view of the fact that the α -substituted cyclic carbonyl compounds can form chiral fixed all-carbon quaternary stereocenter by α -arylation, such as compounds **19a-19i**, **26a-26g**, and **29**, which can effectively avoid the racemization of α -aryl compounds and subsequent reduce of optical purity. Moreover, the construction of chiral all-carbon quaternary stereocenter has always been attracted a majority of interests from the field of organic chemistry [52–58], so it is of great significance to design suitable substrates

for such reactions. Hartwig et al. initiated the asymmetric α -arylation of α -fluoroketone **34a** under various catalytic systems. The results showed that all the attempts were either low yield (54%) or low *ee* (72%). They speculated that the enolization of **34a** was less effective when using weak base K_3PO_4 , but α -fluoroketones **34b** could be completely enolized in situ by weak base [59]. Based on the systematic screening of the catalytic conditions, Hartwig et al. found that the asymmetric coupling of α -fluoroketones (**34b-34c**) with different aryl bromides (**25b** and **35a-35e**) could be efficiently realized under the catalysis of TMEDA· $\text{PdMe}_2/(\text{S})$ -Difluorophosto which gave α -arylation product (**36a-36f**) (Scheme 16) [60].

As a scope extension, Hartwig et al. found that α -fluoro ketones **34d** and **34e** showed good compatibility. Under the catalysis of $\text{Pd}(\text{dba})_2/(\text{R})\text{-L-14}$ or $(\text{S})\text{-segphos}$, **34d** and **34e** could react with different aryl bromides or phenolic trifluoromethanesulfonate to form α -arylated products (**36g-36l**) with excellent *ee* values (Scheme 17). Notably, pyridine, indole, and other nitrogen-containing aryl fragments could be well controlled [60].

Scheme 12 Enantioselective α -C(sp³)-H arylations of cyclic ketones reported by Hartwig et al.

α -Arylation of lactam is more challenging due to its α -hydrogen is less acidic. In 1998, Hartwig et al. first reported palladium catalyzed α -arylation of γ -lactam **37a**. In this study, under a harsh condition of strong base (KHMDS) and high reaction temperature (100 °C), α -arylation product **39a** was obtained in 49% yield using Pd(dba)₂/BINAP catalytic system (Scheme 18, A) [61]. Later, Cossy et al. described palladium catalyzed α -arylation of δ -lactam **37b** in the presence of ZnCl₂, resulting in 85% yield of α -arylation product **39b** at a lower temperature (Scheme 18, B) [62]. Very recently, Stoltz et al. reported an enantioselective α -arylation of γ -lactam using Pd₂(pmdba)₃/L-15 or L-16 (Scheme 19) [63].

Oxindoles are a kind of small lactam molecules with important biological activities. The C3-position (α -position of carbonyl) aryl substituted small molecule oxindoles are promising agents for clinical use [64]. However, due to the higher pK_a value of C3-hydrogen (ca. 18.5) [61], it is hard to deprotonate to form enol, which makes the arylation of C3-position more limited. Willis et al. systematically screened the C3-arylation conditions of *N*-methyl-oxindole **43a** leading to a catalytic system of Pd(dba)₂/XPhos/KHMDS/THF/Toluene. Under this condition, *N*-substituted oxindole (**43a-43b**) were successfully arylated at C3 position

with different aryl bromides (**15**, **18b**, **25c**, **38**, and **44a**) to give corresponding products (**45a-45f**) (Scheme 20) [65].

Meanwhile, Buchwald et al. reported C3-arylations of *N*1 unprotected oxindoles (**46a-46c**) under a similar catalytic system using aryl chlorides (**47a-47f**) as aryl sources and Cs₂CO₃ as base to furnish C3 arylated products (**48a-48f**), in which (**48e-48f**) smoothly formed C3 all-carbon quaternary stereocenters (Scheme 21) [66]. Recently, Hartwig et al. reported the C3 asymmetric arylation of 3-fluoroxindoles (**49a-49e**) based on their previous studies of α -fluoroketones [60] using phenolic trifluoromethanesulfonate (**50a-50b**) as the aryl sources (Scheme 22) [67].

Buchwald et al. studied the asymmetric arylation of C3-methyl oxindoles. They revealed that C3-arylated product **48f** of 3-methyl oxindole **46c** could not be obtained by using aryl chloride **47f** under Pd₂(dba)₃/XPhos/Cs₂CO₃ catalytic system in THF, but could be got under the Pd₂(dba)₃/RuPhos/*t*BuONa system with aryl bromide **25b** in toluene (Scheme 23) [66]. Further optimization led to asymmetric arylation of 1,3-dimethyloxindole **52a** with different aryl or vinyl bromides (**44a** and **53a-53d**) in the presence of TMEDA·PdMe₂/(*S,S*)-L-17 giving the C3 arylated products (**54a-54f**) with high ee values (94–97%) [68].

Direct introduction of *N* atom into the reaction system can greatly promote the reaction by forming the Pd–N complex

Scheme 13 α -C(sp³)-H arylations of various cyclic ketones reported by Buchwald et al.

stabilizing the intermediate transition state and probably also activating the substrate [69–72]. Dong et al. found that palladium catalytic system could be combined with pyrrolidine to effectively achieve the α -arylation of cyclopentanones **55a**. In Pd(OAc)₂/P(*o*-tol)₃/pyrrolidine/AcONa system, some problematic aryl bromides (**56a–56f**) were well tolerable (Scheme 24) [73].

α -Substituted amino acids are a kind of importantly small bioactive molecules, which are fascinating tools to explore the biological process [74, 75]. Among them, the α -arylations of amino acids are usually prepared based on the pre-cyclic derivatives. Hartwig et al. first reported the α -arylation of amino acid derived lactones. It has been found

that the use of bulky electro-rich ligands such as Ad₂PtBu and Q-Phos could greatly improve the reaction efficiency giving α -arylated products (**60a–60e**) with high yields (Scheme 25) [76]. Clayden et al. examined α -arylations of cyclic amino acids hydantoin derivatives (**61a–61c**) under the Pd(TFA)₂/L-9 catalytic system using aryl iodides (**62a–62c**) as aryl sources. They found α -arylated products (**63a–63e**) could be obtained in good yields through ZnF₂-mediated transmetalation (Scheme 26) [77].

Lactones are ubiquitous bioactive precursors of diols and relative analogues. Similar to lactams, conditions that involved strong base are often used to generate the enolates which may decrease the stereo-selectivity of α -arylation.

$\text{Ketone (R}_1\text{)} + \text{ArBr (R}_2\text{)} \xrightarrow[\text{tBuONa, toluene, RT}]{\text{Pd}_2(\text{dba})_3 (1 \text{ mol\%}), \text{Ligand (2.5 mol\%)}}$

24a-24c **15, 18b, 25a-25c** (200 mol%) **26a-26g**

(S)-L-11 **(S)-L-12** **(S)-L-13**

Entry	Ketone (R ₁)	ArBr (R ₂)	Ligand	Yield (%)	ee (%)	Entry	Ketone (R ₁)	ArBr (R ₂)	Ligand	Yield (%)	ee (%)
1	24a(Me)	18b (3-Me)	L12	26a(82)	89	6	24a(Me)	25c(4-MeO)	L12	26d(82)	87
2	24a(Me)	18b (3-Me)	L13	26a(85)	94	7	24a(Me)	15 (4- <i>t</i> Bu)	L11	26e(88)	86
3	24a(Me)	25a(4-Me)	L12	26b(83)	87	8	24a(Me)	15 (4- <i>t</i> Bu)	L13	26e(84)	93
4	24a(Me)	25a(4-Me)	L13	26b(84)	93	9	24b(nPr)	18b (3-Me)	L13	26f(85)	88
5	24a(Me)	25b(3-O Me)	L12	26c(81)	84	10	24c(nPent)	18b (3-Me)	L13	26g(86)	91

Scheme 14 Improvements on arylation α -C(sp³)-H of cyclic ketones reported by Buchwald et al.

Scheme 15 Enantioselective total synthesis of (–)-taiwaniaquinone H and (–)-taiwaniaquinol B

Pd-catalyzed α -arylation of lactone **64** with aryl bromides (**18a**, **25b**, **44a**, and **65a-65f**) was developed by Jansat et al. using (*S*)-mandelic acid as a chiral auxiliary. In this Pd-catalyzed system, bulky P(*t*Bu)₃ also showed a pivotal effect

in both yields and stereo-selectivity, giving corresponding arylated products (**66a-66j**) (Scheme 27) [78]. Zhou et al. reported an elegant study of Pd-catalyzed enantioselective α -arylations of lactone silyl enolates (**67a-67c**) with

Scheme 16 Enantioselective $\alpha\text{-C}(\text{sp}^3)\text{-H}$ arylations of α -fluoro ketones reported by Hartwig et al.

Scheme 17 Enantioselective $\alpha\text{-C}(\text{sp}^3)\text{-H}$ arylations of α -fluoro-1-indanone

phenolic trifluoromethanesulfonates (**68a-68f**) at ambient temperature. Intriguingly, some sterically hindered aryl substrates (**69b-69e**) were well compatible (Schemes 28 and 29) [41].

Difficulties of $\alpha'\text{-C}(\text{sp}^3)\text{-H}$ arylations of cyclic α, β -unsaturated ketones are manifold. Affected by the conjugated

system, the dienolates formed from cyclic ketenes are less nucleophilic than the corresponding enolates. In which, cyclic vinylogous ester (3- or β -alkoxy substituted cyclic α, β -unsaturated ketone) is more electron-rich thereby its dienolate is hardly formed by deprotonation. Furthermore, the dienolates are easy to polymerize with itself, further

Scheme 18 α -C(sp³)-H arylations of Lactams reported by Hartwig et al. (A) and Cossy et al. (B)

reducing the concentration of reaction substrate [79]. Zhang et al. first reported the α' -arylations of 3-alkoxy-2-cyclohexenones (**70a–70c**) using Pd(OAc)₂/BINAP catalyst system in corporation with strong base NaHMDS (Scheme 29), which facilitated the total synthesis of the natural product mesembrine (Scheme 30, Route A) [80]. Shao et al. developed an asymmetric allylation based on common intermediate **73** further leading to the enantioselective total syntheses of (–)-mesembrine and (+)-oxomaritidine (Scheme 30, Route B) [81].

To overcome the limitation of aryl sources in this reaction, Lautens et al. screened different palladium catalysts, and finally found that products (**83a–83f**) could be generated with high yield using the Palladium precatalyst Pd-P(tBu)₃-G2, and α' arylation could be realized at room temperature (Scheme 31) [82]. The α' -arylation of 3-ethoxy-2-cyclohexenone can also be effectively promoted by using the bulky base [83] or phosphine ligand with large steric hindrance [84].

2.2 Nickel-Catalyzed α -C(sp³)-H Arylations of Cyclic Carbonyl Compounds

As a non-noble metal, nickel has also been reported to promote the α -aromatization of cyclic carbonyl compounds. The mechanism of Ni-catalyzed arylation of carbonyl compounds is proved to undergo a similar catalytic cycle with those of Pd-catalyzed arylation (Scheme 2) [85]. In 1973, Semmelhack et al. reported an intramolecular α -arylation of intermediate **84** catalyzed by Ni(COD)₂, thus completing the total synthesis of cephalotaxinone (Scheme 32) [86].

In 2002, Buchwald et al. first reported the Ni-catalyzed intermolecular α -arylation of α -methyl substituted γ -lactones (**85a–85c**), and the asymmetric α -arylation produced **87a–87h** with high *ee* values (Scheme 33) [87].

Later, Chan group reported a Ni-catalyzed asymmetric α -arylation of 2-methyl-2,3-dihydro-1H-inden-1-one (**88a**), 2-methyl-3,4-dihydronaphthalen-1(2H)-one (**88b**), and 6-methyl-6,7,8,9-tetrahydro-5H-benzo annulen-5-one (**88c**) with aryl bromide or iodide (**89a–89 g**). The catalytic

system has good control over six-membered ring substrates, but poor control over five-membered and seven-membered ring substrates (Scheme 34) [88]. It is worth noting that a negative contribution of ZnBr₂ to the catalytic system was observed in this work, which is contrary to the results of Buchwald et al. [87]. Hartwig et al. found that the reaction efficiency and enantioselectivity of 2-methyl-3,4-dihydronaphthalen-1(2H)-one can be significantly improved by using electron deficient phenolic trifluoromethanesulfonate as aryl source under the Ni(COD)₂ (5 mol%)/(*R*)-Difluorophos (6 mol%) catalytic system [20]. On this basis, they further studied the relationship between the catalytic system with the aryl sources, and found that Ni(COD)₂, (*R*)-BINAP, and benzonitrile could form the catalytic active species [(*R*)-BINAP]·Ni(η^2 -NCPh). Using the active species as catalyst, the α -arylation product of 2-methyl-3,4-dihydronaphthalen-1(2H)-one can be obtained with quantitative optical purity (*ee* > 99%) [89]. Recently, it has been reported that α -arylated products with better yields and higher *ee* values could also be obtained using aryl pivalate by Martin et al. [90] or indole substrate by Stanley et al. [91] under the Ni(COD)₂/chiral ligands catalytic system.

2.3 Other Metal Catalyzed α -C(sp³)-H Arylations of Cyclic Carbonyl Compounds

In 2011, MacMillan et al. reported a Cu(I)-catalyzed α -arylation of enol silyl ether based on δ -lactone **91**. The authors speculated that the highly active Cu(III) species in situ formed by the oxidation and insertion of diaryl iodonium salt promoted the reaction, which further underwent the oxidative addition and reductive elimination with enol silyl ether to furnish the final products (**92a–92c**) (Scheme 35) [92].

The corresponding enolates of carbonyl compounds are easily oxidized by oxidants, such as Cu(II), Fe(III) and so on, to form the α -radicals, which can couple with aryl radicals to give α -arylated products. Baran et al. realized the oxidative coupling reaction of optically pure cyclic ketones (**93a–93d**) with indole **94a** and **94b** by using Cu(II) 2-ethylhexanoate

Scheme 19 Pd-catalyzed enantioselective α -arylation of γ -lactams by Stoltz et al.

Scheme 20 C3(sp³)-H arylations of *N*-substituted oxindole reported by Willis et al.

Scheme 21 C3(sp³)-H arylations of *N*1 unprotected oxindole reported by Buchwald et al.

(150 mol%), and the corresponding α -arylated products (**95a-95d**) were obtained in moderate yields (Scheme 36) [93–95]. With the method, they further completed the asymmetric syntheses of natural products (+)-hapalindole Q, (+)-welwitindolinone A, (+)-fischerindoles I, and (+)-ambiguine H starting from the α -arylated products (**95a-95d**).

Later, Li et al. group reported a Fe(III)-catalyzed arylation of 3-substituted oxindoles (**96a-96f**). They believed that the arylation was realized through the addition of free radical in situ generated by Fe(III) or molecular oxygen at C3 position to aryl groups. Moreover, this method was well suitable for preparation of C3-arylated products with largely steric hinderance like **97a-97f** (Scheme 37) [96].

Feng et al. first described an asymmetric arylation of 3-substituted oxindole catalyzed by Sc(OTf)₃/**L-21**. The

asymmetric arylation of 3-substituted oxindoles was carried out under mild conditions, and the product **99a-99d** with excellent optical purity (*ee* > 98%) was obtained (Scheme 38) [97].

Umpolung reactions have been developed as unconventional methods for the synthesis of biologically active target molecules, although the umpolung arylation of cyclic enamines have been much less investigated. Miyata et al. first developed of an efficient umpolung reaction by polarity inversion at the β -position of *N*-alkoxyenamines **101**, which allowed α -arylation of various cyclic ketones **100** under mild conditions (Scheme 39) [22].

$\text{Oxindole } 49\text{a-}49\text{e} + \text{ArOTf } (R_3) \xrightarrow[12\text{mol\% } (R)\text{-Segphos}]{10\text{mol\% Pd(dba)}_2, \text{K}_3\text{PO}_4, \text{toluene, } 50^\circ\text{C}} \text{Product } 51\text{a-}51\text{f}$

Entry	Oxindole (R ₁ R ₂)	ArOTf (R ₃)	Yield (%)	ee (%)	Entry	Oxindole (R ₁ R ₂)	ArOTf (R ₃)	Yield (%)	ee (%)
	49a	50a	51a			49c	50b		
1	(R ₁ =5-Me, R ₂ =Me)	(R ₂ =4-CN)	(97)	93	4	(R ₁ =5-F, R ₂ =Bn)	(R ₂ =4-CO ₂ Me)	51d (67)	95
2	49a	50b	51b	83	5	49d	50a	51e (89)	96
	(R ₁ =5-Me, R ₂ =Me)	(R ₂ =4-CO ₂ Me)	(69)			(R ₁ =H, R ₂ =Bn)	(R ₂ =4-CN)		
	49b	50a	51c			49e	50b		
3	(R ₁ =5-OMe, R ₂ =Me)	(R ₂ =4-CN)	(74)	95	6	(R ₁ =H, R ₂ =Ph)	(R ₂ =4-CO ₂ Me)	51f (71)	80

Scheme 22 Asymmetric C3(sp³)-H arylations of 3-fluoroxindole reported by Hartwig et al.

3 Transition-Metal-Free α -C(sp³)-H Arylations of Cyclic Carbonyl Compounds

Benzyne has high electrophilicity and is easily attacked by nucleophiles to form arylated products. As early as 1966, Ueda et al. reported the α -arylation through the intermediate of benzyne [98]. In the total synthesis of lycorane, they treated the intermediate **107a** with lithium piperidine to form the intermediate **107a'**, which underwent intramolecular addition to form the α -arylated product **108** (Scheme 40). Later, the benzyne-based arylation was applied to α -arylation of lactam [99], asymmetric α -arylation of cyclic ketone in the presence of organic small molecular amines [100]. However, the biggest problem of this method is the regioselectivity of addition to benzyne, which is difficult to apply in multiple substituted aromatic substrates.

Photo-initiated S_{RN}1 aromatization is an effective method for arylation of carbonyl compounds, which was first applied to the total synthesis of cephalotaxinone by semmelhack et al. [79]. Recently, Xia et al. reported the visible-light-promoted the 3-position arylation of 3-substituted oxindoles. They proved that the reaction followed the S_{RN}1 pathway through the activation of aryl iodide. The method has the advantages of wide substrate compatibility (**111a-111f**), high yield (68–85%), and easy operation (Scheme 41) [101].

Jørgensen et al. first reported the α -arylation of cyclic 1,3-diketone **112a** by using phase transfer catalyst (PTC) through the nucleophilic aromatic substitution (S_NAr) reaction with electron deficient benzene **113a** (Scheme 42, A) [102]. Later they found quinine could also promote such transformation when using 1,4-quinone **113b** as aryl source (Scheme 42, B) [103]. Maruoka et al. successfully achieved

Scheme 23 Asymmetric arylation of 1,3-dimethyl oxindole reported by Buchwald et al.

Scheme 24 α -C(sp³)-H arylations of cyclopentanone reported by Dong et al.

Scheme 25 α -(sp^3)-H arylations of oxazol-5-ones by Hartwig et al.

Scheme 26 α -(sp^3)-H arylations of hydantoins reported by Claden et al.

Scheme 27 Enantioselective α -C(sp³)-H arylation of lactone reported by Jansat et al.

Scheme 28 Enantioselective α -C(sp³)-H arylation of lactone-based silyl enolates by Zhou et al.

Scheme 29 α' -(sp³)-H arylation of 3-alkoxy-2-cyclohexenones reported by Zhang et al.

Scheme 30 Total syntheses of mesembrine and oxomaritidine by Zhang (Route A) and Shao (Route B) et al.

Scheme 31 α '-C(sp³)-H arylations of 3-ethoxyl-2-cyclohexenone reported by Lautens et al.

Scheme 32 Intramolecular α -arylation of intermediate **84** reported by Semmelhack et al.

3-position asymmetric arylation of oxindole by the reaction of 3-substituted oxindoles (**115a-115c**) with electron deficient fluorinated aryl compounds (**116a-116c**) under the catalysis of (*S*)-PTC2 (5 mol%). The arylated products (**117a-117e**) was obtained in high yields with excellent *ee* values (Scheme 43) [104]. Subsequently, Kumar et al. found that reaction of *N*-methyloxindole and nitrobenzene in DMSO using *t*BuONa as base, the 3-arylation product

Scheme 33 Enantioselective α -C(sp³)-H arylations of α -substituted γ -lactones

Entry	Substrate(n)	ArXR ₂	Yield (%)	ee (%)	Entry	Substrate(n)	ArXR ₂	Yield (%)	ee (%)
1	88a (n=0)	89a (X=Br, R ₂ =H)	90a (78)	88	5	88b (n=1)	89e (X=I, R ₂ =H)	90e (97)	92
2	88b (n=1)	89b (X=Br, R ₂ =4-tBu)	90b (92)	95	6	88b (n=1)	89f (X=Cl, R ₂ =H)	90f (59)	91
3	88b (n=1)	89c (X=Br, R ₂ =4-CN)	90c (94)	98	7	88c (n=2)	89a (X=Br, R ₂ =H)	90g (70)	73
4	88b (n=1)	89d (X=Br, R ₂ =3-CN)	90d (79)	95	8	88b (n=1)	89g (X=Br, R ₂ =4-CF ₃)	90h (66)	70

Scheme 34 Ni-catalyzed Enantioselective α -C(sp³)-H arylation of α -methyl cyclic ketone

Entry	product	Yield (%)	ee (%)	Entry	product	Yield (%)	ee (%)
1	92a	92a (89)	88	3	92c	92c (76)	91
2	92b	92b (79)	90				

Scheme 35 Cu-catalyzed α' -C(sp³)-H arylations of δ -lactone-based enol silyl ether

Entry	Substrate1 (R ₁)	Substrate2 (R ₂)	product	Yield (%)	Entry	Substrate1 (R ₁)	Substrate2 (R ₂)	product	Yield (%)
1	93a	94a(R ₂ =H)	95a	95a(53)	3	93c	94b(R ₂ =Br)	95c	95c(50)
2	93b	94a(R ₂ =H)	95b	95b(55)	4	93d	94b(R ₂ =Br)	95d	95d(62)

Scheme 36 Enantioselective α -C(sp³)-H arylations of cyclic ketones reported by Baran et al.

Scheme 37 Fe-catalyzed arylation of 3-substituted oxindole reported by Li et al.

could be obtained in good yields. They also proved that the reaction was realized by the addition of oxindole anion to nitrobenzene [105].

Anyang et al. reported a α -arylation of cyclic α -nitroketone **118** with various diaryl iodonium salts which

are environmental friendly, easy to prepare, and stable. α -Arylated products (**119a–119j**) were obtained in moderate to high yields (Scheme 44) [106].

Scheme 38 Asymmetric C3-arylations of 3-substituted oxindoles reported by Feng group

Scheme 39 α -C(sp³)-H arylations through umpolung reaction

Scheme 40 Total synthesis of lycorane via intramolecular addition of benzyne

Scheme 41 visible-light-promoted C3-arylations of 3-substituted oxindoles reported by Xia et al.

Scheme 42 α -C(sp³)-H arylations of cyclic 1,3-diketones catalyzed by PTC (A) and quinine (B)

(B).

Entry	Substrate (R ₁)	ArIR ₂	product	Yield (%)	ee (%)	Entry	Substrate (R ₁)	ArIR ₂	product	Yield (%)	ee (%)
1	115a (R ₁ =H)	116a (R ₂ =H)	117a	(99)	91	3	115a (R ₁ =H)	116b (R ₂ =Br)	117c	(93)	93
2	115b (R ₂ =Me)	116a (R ₂ =H)	117b	(86)	94	4	115c (R ₂ =MeO)	116a (R ₂ =H)	117d	(91)	92

Scheme 43 Asymmetric C3-arylations of 3-substituted oxindoles reported by Maruoka et al.

Entry	Ar ₁ /Ar ₂	Yield (%)	Entry	Ar ₁ /Ar ₂	Yield (%)
1	Ar ₁ =Ar ₂ =Ph	119a (80)	6	Ar ₁ =Ar ₂ =4-CF ₃ -Ph	119f (76)
2	Ar ₁ =Ar ₂ =3-Cl-Ph	119b (80)	7	Ar ₁ =Ar ₂ =3-CF ₃ -Ph	119g (50)
3	Ar ₁ =Ar ₂ =4-Cl-Ph	119c (75)	8	Ar ₁ =Ar ₂ =4- ⁱ Bu-Ph	119h (48)
4	Ar ₁ =Ar ₂ =3-Br-Ph	119d (77)	9	Ar ₁ =Ar ₂ =4-OMe-Ph	119i (59)
5	Ar ₁ =Ar ₂ =4-Br-Ph	119e (73)	10	Ar ₁ =Ar ₂ =3-F-Ph	119j (53)

Scheme 44 α -C(sp³)-H arylation of cyclic α -nitroketones with diaryl iodonium salts

4 Conclusion

In recent years, α -C(sp³)-H arylation of cyclic carbonyl compounds has made a great progress, which provides many simple and effective methods for syntheses of molecules for biological tool, active natural products, and drugs, etc., such as 3-aryl 3-fluoroindoles, etc.. However, most of the asymmetric methods are limited to transition metal catalytic systems, problems such as how to realize green procedures

and relatively small range of substrates remains to investigate. For example, Ni(0) catalyst is highly toxic, aryl halides with *ortho* hindered substituent have low compatibility in palladium catalytic system [107], asymmetric α -arylation of amino acids, and control of α -C(sp³)-H arylation through free radical process, etc., need to be solved.

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References

1. J. Ren, X. Shi, X.N. Li, L.W. Li, J. Su, L.D. Shao, Q.S. Zhao, *Org. Lett.* **18**, 3948–3951 (2016)
2. J. Rodrigalvarez, M. Nappi, *Nat. Chem.* **12**, 76–81 (2020)
3. J. Zhao, T. Nanjo, *Nat. Chem.* **11**, 213–221 (2019)
4. K.J. Jiao, Y.K. Xing, Q.L. Yang, *Acc. Chem. Res.* **53**, 300–310 (2020)
5. F. Berger, M.B. Plutschack, J. Riegger, W. Yu, S. Speicher, M. Ho, N. Frank, T. Ritter, *Nature* **567**, 223–228 (2019)
6. K. Feng, R.E. Quevedo, J.T. Kohrt, M.S. Oderinde, U. Reilly, M.C. White, *Nature* **580**, 621–627 (2020)
7. F. de Azambuja, M.H. Yang, T. Feoktistova, M. Selvaraju, A.C. Brueckner, M.A. Grove, S. Koley, P.H. Cheong, *Nat. Chem.* **12**, 489–496 (2020)
8. Y. Zhu, L.D. Shao, Z.T. Deng, Y. Bao, X. Shi, Q.S. Zhao, *J. Org. Chem.* **83**, 10166–10174 (2018)
9. M.C. White, J. Zhao, *J. Am. Chem. Soc.* **140**, 13988–14009 (2018)
10. P.J. Sarver, V. Bacauanu, D.M. Schultz, D.A. DiRocco, Y. Lam, E.C. Sherer, D.W.C. MacMillan, *Nat. Chem.* **12**, 459–467 (2020)
11. J. Xu, L.D. Shao, D.S. Li, X. Deng, Y.C. Liu, Q.S. Zhao, C. Xia, *J. Am. Chem. Soc.* **136**, 17962–17965 (2014)
12. S. Rej, Y. Ano, N. Chatani, *Chem. Rev.* **120**, 1788–1887 (2020)
13. H. Renata, Q. Zhou, P.S. Baran, *Science* **339**, 59–63 (2013)
14. B.R. Rosen, L.R. Simke, P.S. Thuy-Boun, D.D. Dixon, J.Q. Yu, P.S. Baran, *Angew. Chem. Int. Ed.* **52**, 7317–7320 (2013)
15. H. Renata, Q. Zhou, G. Dunstl, J. Felding, R.R. Merchant, C.H. Yeh, P.S. Baran, *J. Am. Chem. Soc.* **137**, 1330–1340 (2015)
16. K. Godula, D. Sames, *Science* **312**, 67–72 (2006)
17. J. He, M. Wasa, K.S.L. Chan, Q. Shao, J.Q. Yu, *Chem. Rev.* **117**, 8754–8786 (2017)
18. C.C.C. Johansson, T.J. Colacot, *Angew. Chem. Int. Ed.* **49**, 676–707 (2010)
19. D. Vargová, I. Némethová, K. Plevová, R. Šebesta, *ACS Catal.* **9**, 3104–3143 (2019)
20. A. Ehrentraut, A. Zapf, M. Beller, *Adv. Synth. Catal.* **344**, 209–217 (2002)
21. D.A. Culkin, J.F. Hartwig, *Acc. Chem. Res.* **36**, 234–245 (2003)
22. F. Bellina, R. Rossi, *Chem. Rev.* **110**, 1082–1146 (2010)
23. S.T. Sivanandan, A. Shaji, I. Ibnuaud, C.C.C.J. Seechurn, T.J. Colacot, *Eur. J. Org. Chem.* **2015**, 38–49 (2015)
24. Y.J. Hao, X.S. Hu, Y. Zhou, J. Zhou, J.S. Yu, *ACS Catal.* **10**, 955–993 (2020)
25. T. Murahashi, H. Kurosawa, *J. Organomet. Chem.* **574**, 142–147 (1999)
26. M.A. Ciufolini, H.B. Qi, M.E. Browne, *J. Org. Chem.* **53**, 4149–4151 (1988)
27. H. Muratake, M. Natsume, *Tetrahedron Lett.* **38**, 7581–7582 (1997)
28. M.K.M. Tun, D.J. Wüsthmann, S.B. Herzon, *Chem. Sci.* **2**, 2251–2253 (2011)
29. L. Fan, S. Takizawa, Y. Takeuchi, K. Takenaka, H. Sasai, *Org. Biomol. Chem.* **13**, 4837–4840 (2015)
30. T. Wu, X. Kang, H. Bai, W. Xiong, G. Xu, W. Tang, *Org. Lett.* **22**, 4602–4607 (2020)
31. D. Solé, L. Vallverdú, X. Solans, M. Font-Bardia, J. Bonjoch, *J. Am. Chem. Soc.* **125**, 1587–1594 (2003)
32. R.R. Liu, B.L. Li, J. Lu, C. Shen, J.R. Gao, Y.X. Jia, *J. Am. Chem. Soc.* **138**, 5198–5201 (2016)
33. M. Wang, J. Chen, Z. Chen, C. Zhong, P. Lu, *Angew. Chem. Int. Ed.* **57**, 2707–2711 (2018)
34. C. Zhu, D. Wang, Y. Zhao, W.Y. Sun, Z. Shi, *J. Am. Chem. Soc.* **139**, 16486–16489 (2017)
35. X. Huang, W.R.J.J. Oh, J.S. Zhou, *Angew. Chem. Int. Ed.* **57**, 7673–7677 (2018)
36. M. Palucki, S.L. Buchwald, *J. Am. Chem. Soc.* **119**, 11108–11109 (1997)
37. A. Svennebring, N. Garg, P. Nilsson, A. Hallberg, M. Larhed, *J. Org. Chem.* **70**, 4720–4725 (2005)
38. M. Storgaard, F.Z. Dörwald, B. Peschke, D. Tanner, *J. Org. Chem.* **74**, 5032–5040 (2009)
39. É. Bélanger, K. Cantin, O. Messe, M. Tremblay, J.F. Paquin, *J. Am. Chem. Soc.* **129**, 1034–1035 (2007)
40. D. Solé, L. Vallverdú, X. Solans, M. Font-Bardia, J. Bonjoch, *J. Am. Chem. Soc.* **125**, 1587–1594 (2003)
41. Z. Huang, Z. Chen, L.H. Lim, G.C.P. Quang, H. Hirao, J. Zhou, *Angew. Chem. Int. Ed.* **52**, 5807–5812 (2013)
42. J. Åhman, J.P. Wolfe, M.V. Troutman, M. Palucki, S.L. Buchwald, *J. Am. Chem. Soc.* **120**, 1918–1919 (1998)
43. M. Kawatsura, J.F. Hartwig, *J. Am. Chem. Soc.* **121**, 1473–1478 (1999)
44. X. Liao, Z. Weng, J.F. Hartwig, *J. Am. Chem. Soc.* **130**, 195–200 (2008)
45. C. Richter, K.V.S. Ranganath, F. Glorius, *Adv. Synth. Catal.* **354**, 377–382 (2012)
46. J.M. Fox, X. Huang, A. Chieffi, S.L. Buchwald, *J. Am. Chem. Soc.* **122**, 1360–1370 (2000)
47. M.S. Viciu, R.F. Germaneau, S.P. Nolan, *Org. Lett.* **4**, 4053–4056 (2002)
48. T. Hamada, A. Chieffi, J. Åhman, S.L. Buchwald, *J. Am. Chem. Soc.* **124**, 1261–1268 (2002)
49. C.I. Chang, J.Y. Chang, C.C. Kuo, W.Y. Pan, Y.H. Kuo, *Planta Med.* **71**, 72–76 (2005)
50. W.H. Lin, J.M. Fang, Y.S. Cheng, *Phytochemistry* **40**, 871–873 (1995)
51. X. Liao, L.M. Stanley, J.F. Hartwig, *J. Am. Chem. Soc.* **133**, 2088–2091 (2011)
52. R. Zhan, Y.T. Hu, L.D. Shao, X.J. Qin, F. Kuang, S.Z. Du, F. Wu, Y.G. Chen, *Org. Lett.* **21**, 3678–3681 (2019)
53. N. Wang, S. Du, D. Li, X. Jiang, *Org. Lett.* **19**, 3167–3170 (2017)
54. N. Hu, C. Dong, C. Zhang, G. Liang, *Angew. Chem. Int. Ed.* **58**, 6659–6662 (2019)
55. X. Tong, B. Shi, K. Liang, Q. Liu, C. Xia, *Angew. Chem. Int. Ed.* **58**, 5443–5446 (2019)
56. S. Jansana, F. Diaba, J. Bonjoch, *Org. Lett.* **21**, 5757–5761 (2019)
57. Q. Zhang, F.M. Zhang, C.S. Zhang, S.Z. Liu, J.M. Tian, S.H. Wang, X.M. Zhang, Y.Q. Tu, *J. Org. Chem.* **84**, 12664–12671 (2019)
58. B. Zhang, X. Wang, C. Li, *J. Am. Chem. Soc.* **142**, 3269–3274 (2020)
59. C. Han, E.H. Kim, D.A. Colby, *J. Am. Chem. Soc.* **133**, 5802–5805 (2011)
60. Z. Jiao, J.J. Beiger, Y. Jin, S. Ge, J.S. Zhou, J.F. Hartwig, *J. Am. Chem. Soc.* **138**, 15980–15986 (2016)
61. K.H. Shaughnessy, B.C. Hamann, J.F. Hartwig, *J. Org. Chem.* **63**, 6546–6553 (1998)
62. A. de Filippis, D. Gomez Pardo, J. Cossy, *Tetrahedron Lett.* **60**, 9757–9767 (2004)
63. C.I. Jette, I. Geibel, S. Bachman, M. Hayashi, S. Sakurai, H. Shimizu, J.B. Morgan, B.M. Stoltz, *Angew. Chem. Int. Ed.* **58**, 4297–4301 (2019)
64. P. Hewawasam, V.K. Gribkoff, Y. Pendri, S.I. Dworetzky, N.A. Meanwell, E. Martinez, C.G. Boissard, D.J. Post-Munson, J.T. Trojnacki, K. Yeleswaram, L.M. Pajor, J. Knipe, Q. Gao, R. Perrone, J.E. Starrett, *Bioorg. Med. Chem. Lett.* **12**, 1023–1026 (2002)
65. M.J. Durbin, M.C. Willis, *Org. Lett.* **10**, 1413–1415 (2008)

66. R.A. Altman, A.M. Hyde, X. Huang, S.L. Buchwald, *J. Am. Chem. Soc.* **130**, 9613–9620 (2008)
67. Y. Jin, M. Chen, S. Ge, J.F. Hartwig, *Org. Lett.* **19**, 1390–1393 (2017)
68. A.M. Taylor, R.A. Altman, S.L. Buchwald, *J. Am. Chem. Soc.* **131**, 9900–9901 (2009)
69. Z. Wang, B.J. Reinius, G. Dong, *J. Am. Chem. Soc.* **134**, 13954–13957 (2012)
70. F. Mo, G. Dong, *Science* **345**, 68–72 (2014)
71. H.N. Lim, G. Dong, *Angew. Chem. Int. Ed.* **54**, 15294–15298 (2015)
72. Z. Wang, B.J. Reinius, G. Dong, *Chem. Comm.* **50**, 5230–5232 (2014)
73. Y. Xu, T. Su, Z. Huang, G. Dong, *Angew. Chem. Int. Ed.* **55**, 2559–2563 (2016)
74. D. Obrecht, M. Altorfer, C. Lehmann, P. Schönholzer, K. Müller, *J. Org. Chem.* **61**, 4080–4086 (1996)
75. D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, K. Müller, *Helv. Chim. Acta.* **78**, 563–580 (1995)
76. X. Liu, J.F. Hartwig, *Org. Lett.* **5**, 1915–1918 (2003)
77. F. Fernández-Nieto, J. Mas Roselló, S. Lenoir, S. Hardy, J. Clayden, *Org. Lett.* **17**, 3838–3841 (2015)
78. L. Jiang, S. Weist, S. Jansat, *Org. Lett.* **11**, 1543–1546 (2009)
79. A.M. Hyde, S.L. Buchwald, *Angew. Chem. Int. Ed.* **47**, 177–180 (2008)
80. Y. Zhao, Y. Zhou, L. Liang, X. Yang, F. Du, L. Li, H. Zhang, *Org. Lett.* **11**, 555–558 (2009)
81. W. Wang, J. Dai, Q. Yang, Y.H. Deng, F. Peng, Z. Shao, *Org. Lett.* **23**, 920–924 (2021)
82. T. Johnson, F. Pultar, F. Menke, M. Lautens, *Org. Lett.* **18**, 6488–6491 (2016)
83. W.Y. Hou, Y.K. Wu, *Org. Lett.* **19**, 1220–1223 (2017)
84. Y.C. Yang, Y.C. Li, Y.K. Wu, *Org. Lett.* **21**, 9286–9290 (2019)
85. N. Hazari, P.R. Melvin, M.M. Beromi, *Nat. Rev. Chem.* **1**, 0025 (2017)
86. M.F. Semmelhack, R.D. Stauffer, T.D. Rogerson, *Tetrahedron Lett.* **14**, 4519–4522 (1973)
87. D.J. Spielvogel, S.L. Buchwald, *J. Am. Chem. Soc.* **124**, 3500–3501 (2002)
88. G. Chen, F.Y. Kwong, H.O. Chan, W.Y. Yu, A.S.C. Chan, *Chem. Commun.* **7**, 1413–1415 (2006)
89. S. Ge, J.F. Hartwig, *J. Am. Chem. Soc.* **133**, 16330–16333 (2011)
90. E.P.J. Josep Cornella, R. Martin, *Angew. Chem. Int. Ed.* **54**, 4 (2015)
91. A. Ghosh, J.A. Walker, A. Ellern, L.M. Stanley, *ACS Catal.* **6**, 2673–2680 (2016)
92. J.S. Harvey, S.P. Simonovich, C.R. Jamison, D.W.C. MacMillan, *J. Am. Chem. Soc.* **133**, 13782–13785 (2011)
93. P.S. Baran, J.M. Richter, *J. Am. Chem. Soc.* **126**, 7450–7451 (2004)
94. P.S. Baran, J.M. Richter, *J. Am. Chem. Soc.* **127**, 15394–15396 (2005)
95. P.S. Baran, T.J. Maimone, J.M. Richter, *Nature* **446**, 404–408 (2007)
96. E.A. Hong-Ru Wu, *Chem. Eur. J.* **21**, 5 (2015)
97. J. Guo, S. Dong, Y. Zhang, Y. Kuang, X. Liu, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **52**, 10245–10249 (2013)
98. N. Ueda, T. Tokuyama, T. Sakan, *Bull. Chem. Soc. Jpn.* **39**, 2012–2014 (1966)
99. J.D. Stewart, S.C. Fields, K.S. Kochhar, H.W. Pinnick, *J. Org. Chem.* **52**, 2110–2113 (1987)
100. E. Picazo, S.M. Anthony, M. Giroud, A. Simon, M.A. Miller, K.N. Houk, N.K. Garg, *J. Am. Chem. Soc.* **140**, 7605–7610 (2018)
101. K. Liang, N. Li, Y. Zhang, T. Li, C. Xia, *Chem. Sci.* **10**, 3049–3053 (2019)
102. M. Bella, S. Koppelgaard, K.A. Jørgensen, *J. Am. Chem. Soc.* **127**, 3670–3671 (2005)
103. J. Alemán, B. Richter, K.A. Jørgensen, *Angew. Chem. Int. Ed.* **46**, 5515–5519 (2007)
104. S. Shirakawa, K. Koga, T. Tokuda, K. Yamamoto, K. Maruoka, *Angew. Chem. Int. Ed.* **53**, 6220–6223 (2014)
105. M. Sattar, V. Rathore, C.D. Prasad, S. Kumar, *Chem. Asian J.* **12**, 734–743 (2017)
106. Y. An, X.M. Zhang, Z.Y. Li, W.H. Xiong, R.D. Yu, F.M. Zhang, *Chem. Commun.* **55**, 119–122 (2018)
107. X. Rao, N. Li, H. Bai, C. Dai, Z. Wang, W. Tang, *Angew. Chem. Int. Ed.* **57**, 12328–12332 (2018)