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Transition metal-catalyzed sp³ C–H activation and intramolecular C–N coupling to construct nitrogen heterocyclic scaffolds

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Nitrogen heterocycles are of great medicinal importance, and the construction of nitrogen heterocyclic scaffolds has been one of the focuses in synthetic organic chemistry. Recently, the strategy of transition metal-catalyzed sp³ C–H activation and intramolecular C–N coupling to construct nitrogen heterocyclic scaffolds has been well developed. Palladium, copper, silver, nickel, cobalt, ruthenium and rhodium catalysis were successfully used for the construction of nitrogen heterocyclic scaffolds, aziridines, azetidines, pyrrolidines, pyrrolidine-2,5-diones, indolines, isoindolines, isoindolinones, tetrahydropyridines, oxazolidinones, oxazinanones, β-lactams, γ-lactams *etc.*, which have been synthesized by the sp³ C–H activation strategy. Here, we summarize the progress of transition metal-catalyzed sp³ C–H activation/intramolecular C–N bond formation, and introduce both the reaction development and mechanisms in numerous synthetically useful intramolecular sp³ C–H catalytic aminations/amidations.

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1. Introduction

Nitrogen heterocycles are important structural units in many biologically active natural products and synthetic pharmaceuticals, and thus the construction of nitrogen heterocyclic scaffolds has attracted the attention of many chemists.[1–4] Intramolecular direct amination/amidation of sp³ C–H bonds is an effective method to construct nitrogen heterocyclic scaffolds, and there are thus

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far three main approaches to this problem: (1) rhodium-,[5] iron-,[6] cobalt-,[7] or silver-[8] catalyzed nitrene insertion reaction of sulfamides/carbamates or aryl/alkyl azides, (2) metal-free intramolecular oxidative coupling of sp^3 C–H and N–H,[9–17] and (3) transition metal-catalyzed intramolecular coupling of sp^3 C–H and N–H *via* C–H activation. The first two approaches have limitations, as the products by the first approach are secondary amides or amines and tertiary C–H bonds are preferentially functionalized and benzylic or allylic C–H bonds are aminated in most cases using the second approach; primary C–H bonds are always preferentially functionalized by the third approach, and benzylic or allylic C–H bonds can also be functionalized, so the last approach complements the first two with respect to the reactivity patterns, and it has been well developed in recent years. A variety of metal catalysts have been found to be useful in such reactions, some reactions have been mentioned in recent reviews,[4] but they have less content describing the types of heterocyclic scaffolds constructed and sorts of catalysts related to intramolecular sp^3 C–H amination/ amidation, so it is necessary to write a review to summarize the progress in this field. The following content includes construction of nitrogen heterocyclic scaffolds *via* sp^3 C–H activation and intramolecular C–N coupling under palladium, copper, silver, nickel, cobalt, ruthenium or rhodium catalysis respectively, affording aziridines, azetidines, pyrrolidines, pyrrolidine-2,5-diones, indolines, isoindolines, isoindolinones, tetrahydropyridines, oxazolidinones, oxazinanones, β-lactams, γ-lactams *etc*. Two types of transformations with respect to disconnections will be introduced, one is the direct intramolecular coupling of sp^3 C–H and N–H *via* C–H activation, and the other is carbonylative cyclization *via* sp^3 C–H activation followed by insertion of CO and subsequent C–N coupling.

2. Palladium catalysis

In 2009, Glorius and co-workers reported the pioneering work about the intramolecular amidation of unactivated sp^3 C–H bonds, and indolines were synthesized *via* palladium-catalyzed cyclization of anilines (Scheme 1).[18] An unactivated sp^3 C–H bond is activated with the assistance of an amide directing group, and then the amide nitrogen is coupled with the sp^3 carbon *via* reductive elimination; the transformation proceeded smoothly, affording indolines in good yields up to 80%, and the functional group tolerance is broad, halogen (Br, Cl) is also tolerated, which can be used in further manipulations. This transformation is the first example of the construction of nitrogen heterocyclic scaffolds *via* transition metal-catalyzed unactivated sp^3 C–H bond activation and intramolecular coupling of C–H and N–H, and nitrenes are not required in this transformation.

A Pd(II)/Pd(0) catalytic cycle and a Pd(II)/Pd(IV) catalytic cycle are considered as the possible mechanism for the cyclization of anilines (Scheme 2). Coordination of the aniline 1-1 with Pd(II) gives Pd(II) complex 2-A, subsequent C–H activation gives the six-membered ring Pd(II) complex 2-B, which gives product 1-2 *via* reductive elimination, and the generated Pd(0) species is reoxidized by AgOAc to a Pd(II) species, which completes the Pd(II)/Pd(0) catalytic cycle. The Pd(IV) complex 2-C can be formed *via* the oxidation of 2-B, and the product 1-2 can also be obtained *via* a Pd(II)/Pd(IV) catalytic cycle. It is concluded that

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Junmin Chen

Junmin Chen obtained his MS degree in 2005 from Jiangxi Normal University (China). He earned his doctoral degree at the Chengdu Institute of Organic Chemistry of the Chinese Academy of Science in 2010 under the supervision of Prof. Jian Liao. He became an associate professor at Jiangxi Normal University in 2012. His current research is focused on transition metal-catalyzed C–H bond functionalization and new methods for heterocycle synthesis.
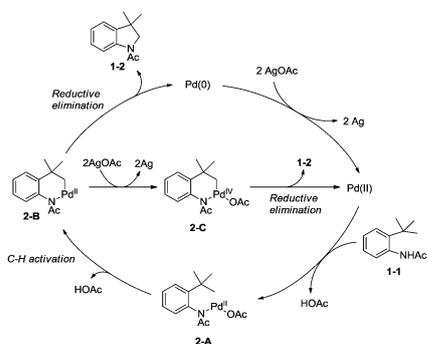
Ai Qin Zhang

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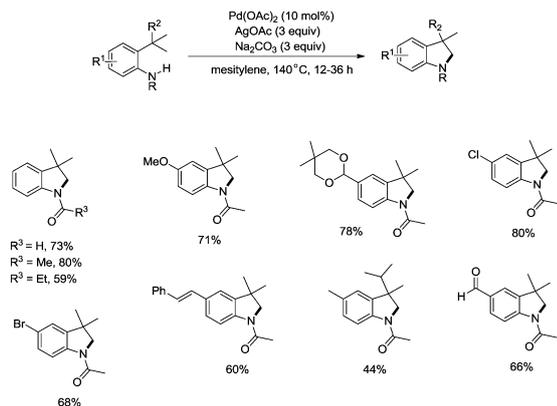
**Scheme 1** Synthesis of indolines by Glorius.

Scheme 2 The mechanism for cyclization of anilines.

a sequential acetoxylation/amidation pathway in this reaction is impossible according to the control experiments.

In 2012, Daugulis and co-workers developed a palladium acetate-catalyzed method for the synthesis of pyrrolidines, indolines, and isoindolines *via* a C–H/N–H coupling (Scheme 3a),[19a] employing a picolinamide directing group. Sp[2] C–H bonds, benzylic sp[3] C–H bonds and C–H bonds of a methyl group are reactive. Methylene can't undergo the amination. The directing auxiliary can be removed by LiEt$_3$BH.

In the same year, Chen and co-workers reported a palladium-catalyzed intramolecular amination of sp[3] C–H and sp[2] C–H bonds, affording azetidines, pyrrolidines, and indolines highly efficiently (Scheme 3b).[19b,c] The *N,N*-bidentate picolinamide was used as a directing group, the sp[3] C–H and sp[2] C–H bonds at the γ or δ positions were activated by the palladium(II) species, and intramolecular C–N bonds were formed *via* reductive elimination. Primary sp[3] C–H bonds of methyl groups on both γ and δ positions could be preferentially functionalized, and certain geminal dimethyl substrates underwent the cyclization smoothly with high diastereoselectivity (dr > 20 : 1) (**3-2a, 3-2e**). The order of C–H activation reactivities of different sp[3] C–H bonds under the reaction conditions was as follow: secondary and tertiary γ-C–H bonds < primary δ-C–H bonds < primary γ-C–H bonds (**3-2b, 3-2c, 3-2d**).

When the *N,N*-bidentate moiety of *N*1-*p*-methyoxyphenyl-1,2,3-triazole-4-carboxylic acid derived amides was used as a
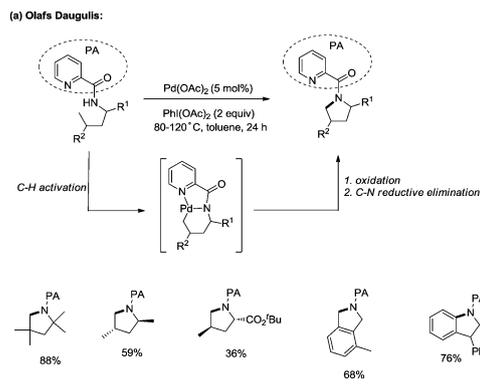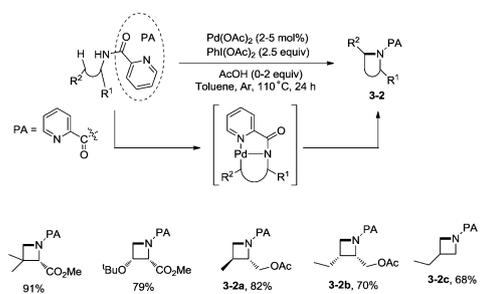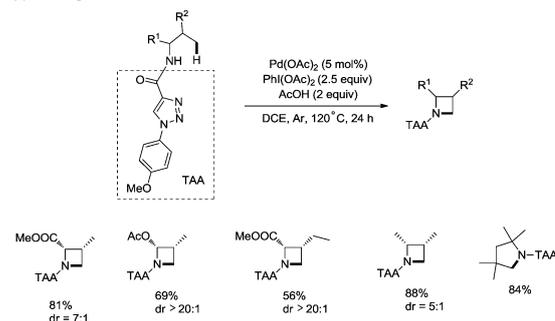

Scheme 3 Formation of cyclic amines.

directing group, sp[3] C–H bonds could also undergo intra-molecular amination under palladium catalysis (Scheme 3c).[19d] The C–H bonds at γ positions were preferentially aminated over those at δ positions, the primary C–H bonds were selectively functionalized over the secondary C–H bonds, and a series of azetidines were obtained successfully. A pyrrolidine was also synthesised in 84% yield with the directing group.
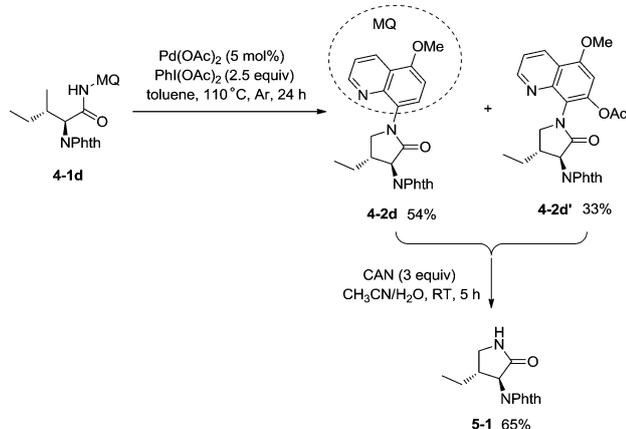
In 2013, Chen and co-workers reported another example of constructing nitrogen heterocycles *via* palladium-catalyzed sp[3] C–H activation/intramolecular coupling of C–H/N–H, affording pyrrolidones (γ-lactams) effectively (Scheme 4).[20] 8-Aminoquinoline or 2-pyridylmethyl amine were used as bidentate directing groups,
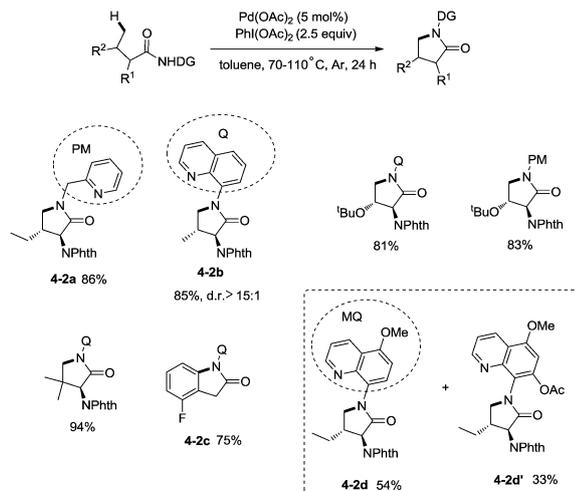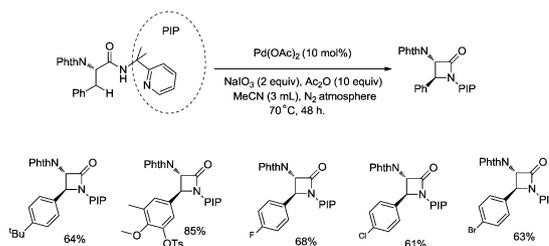
Scheme 4 Palladium-catalyzed intramolecular amination by Chen.

the γ-sp^3 C–H and sp^2 C–H bonds of the amides were activated, forming intramolecular C–N bonds [(4-2a)-(4-2d)], the primary sp^3 C–H bonds of the methyl groups on the γ positions could be preferentially functionalized (4-2a, 4-2d), and the diastereoselectivity is excellent with certain geminal dimethyl substrates (for example, 4-2b, dr > 15 : 1). The 5-methoxyquinolin-8-amine derived substrate 4-1d was converted into a mixture of pyrrolidones (4-2d, 4-2d′). The 5-methoxy-quinolin-8-yl group (MQ) and its derivative of the directing group in the target molecules can be removed readily by treatment with ceric ammonium nitrate (CAN), and the NH pyrrolidone 5-1 was obtained in 65% yield, increasing the applications of the method in synthetic organic chemistry (Scheme 5).

In 2013, Shi and co-workers used an N,N-bidentate directing group containing 2-(pyridin-2-yl)isopropyl (PIP) to achieve β-C(sp^3)–H activation and C–N coupling cyclization, a series of α-amino-β-lactams were stereoselectively synthesized in acceptable yields, and the starting materials (substrates) can be easily prepared via palladium(ɪɪ) acetate-catalyzed sp^3 C–H monoarylation of alanine, undergoing the subsequent intramolecular amidation (Scheme 6).[21] Secondary β-benzylic C–H bonds are amidated in this transformation. While this process is

smooth and functional-group-tolerant, the PIP auxiliary cannot be removed from the β-lactams, which hinders its application in organic synthesis.

In 2017, the same group reported a revised version, where 5-methoxyquinolin-8-amine was used as a directing group, in which the auxiliary group can be removed. Palladium-catalyzed monoarylation of alanine and subsequent amidation of sp^3 C–H bonds were successfully accomplished, affording various α-amino-β-lactams stereoselectively, and the reaction is highly efficient and compatible with a variety of functional groups (Scheme 7).[22] The auxiliary group 5-methoxy-quinolin-8-yl (MQ) in the target molecules can be removed readily by treatment with ceric ammonium nitrate (CAN). Orthogonally protected anti-α,β-diamino acids could be synthesized stereoselectively from α-amino-β-lactams, which is useful to the total synthesis of certain natural products and biologically active compounds (Scheme 8).

In 2013, Zhang reported isoindolinone (9-2) synthesis from 2,6-dimethyl-N-(8-quinolinyl)benzamides 9-1 via palladium-catalyzed intramolecular amidation of primary benzylic C–H bonds using 8-aminoquinoline as a directing group, the N,N-bidentate amide directing group was essential to the transformation (Scheme 9).[23] A possible mechanism was proposed (Scheme 10).
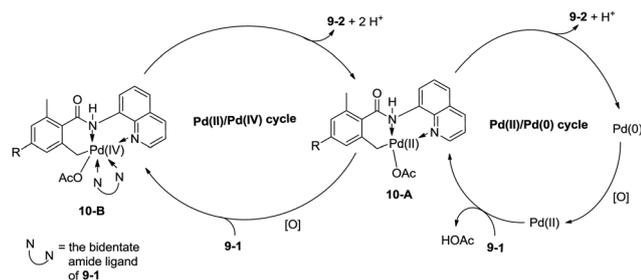

Scheme 6 The intramolecular sp^3 C–H amidation with PIP as the directing group.
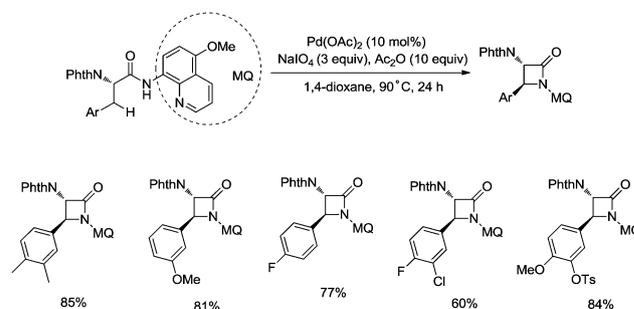
Scheme 7 Palladium-catalyzed intramolecular methylene amidation.

Scheme 5 Removable auxiliary group MQ.
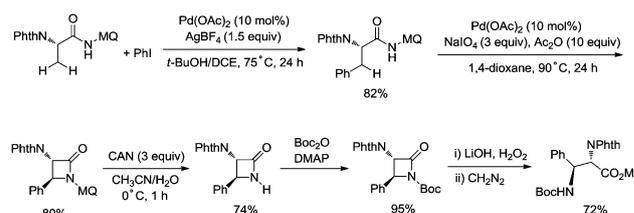
Scheme 8 Synthesis of protected anti-α,β-diamino acids.
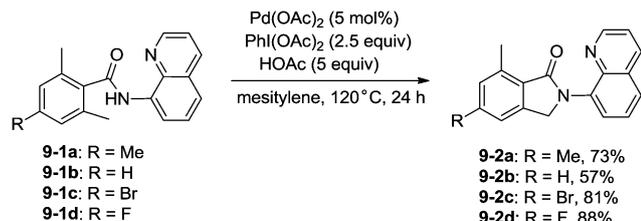
**Scheme 9** Isoindolone synthesis *via* palladium–catalyzed intramolecular amidation.

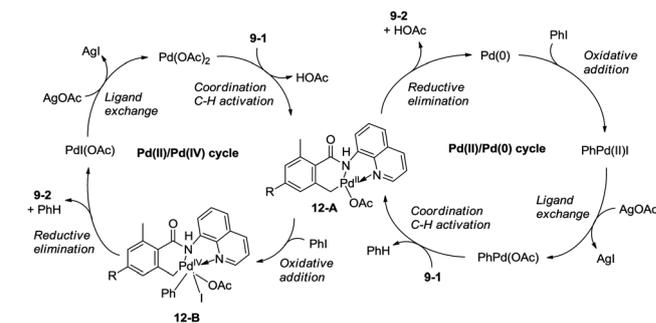**Scheme 10** The possible mechanism for isoindolone synthesis.

Coordination of the bidentate 8-aminoquinoline system **9-1** to palladium and ligand exchange followed by benzylic C–H activation produce a fused five-membered ring and six-membered ring intermediate **10-A**, then reductive elimination gives the product **9-2** and Pd(0), and oxidation of the Pd(0) species by PhI(OAc)$_2$ gives the Pd(ɪɪ) species, which completes the Pd(ɪɪ)/Pd(0) catalytic cycle. A Pd(ɪɪ)/Pd(ɪᴠ) catalytic cycle is also thought to be possible. The intermediate **10-A** is oxidized to the Pd(ɪᴠ) species **10-B**, then reductive elimination gives the product **9-2** and the Pd(ɪɪ) complex **10-A**.

Zhang and co-workers intented to effect palladium-catalyzed arylation of benzylic C–H bonds with 2,6-dimethyl-*N*-(8-quinolinyl)-benzamides **9-1** as substrates according to the literature methods,[24] the cyclization products isoindolinones were obtained in excellent yields *via* intramolecular C–N coupling, and no arylation product was found (Scheme 11).[25] The 8-quinolyl as a directing group and two methyl groups in the *ortho* positions were found to be necessary. Phenyl iodide acted as an oxidant of the catalytic cycles for intramolecular C–N coupling (Scheme 12). The reactions proceed in high yields, and the procedure is easy to perform.

sp^3 C–H bonds were activated by the assistance of *N*-mono-dentate or *N,N*-bidentate amide systems forming five- or six-membered cyclopalladation complexes in the above examples.
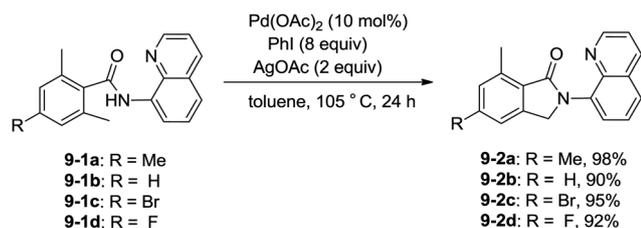
**Scheme 11** Synthesis of isoindolinones with PhI.

**Scheme 12** The possible mechanism for isoindolone synthesis with PhI.

In 2014, aliphatic secondary amines were found to be also useful directing groups, and strained four-membered ring cyclopalladation intermediates were formed (as confirmed by single-crystal X-ray diffraction).[26a] A series of amino-lactones were used as substrates, and the corresponding aziridines were obtained in moderate to good yields (up to 80%) (Scheme 13). This strategy showed that simple aliphatic amines possessing methyl groups adjacent to an unprotected amine nitrogen atom can be converted directly into strained nitrogen heterocycles. The aziridine ring opening with nucleophiles such as azide, thiol, chloride and water afforded fully substituted secondary aliphatic amines (Scheme 14). The product of an aziridine ring opening (**14-1**) provided a new class of secondary aliphatic amines through further conversion (**14-2**, **14-3**), the biological properties of which are worth exploring.

Strained nitrogen heterocycle β-lactams which are important structure units of potential pharmaceutical agents can also be produced *via* carbonylation of the sp^3 C–H bonds of a methyl group adjacent to a secondary amine, and this further demon-strates the broad uses of the C–H activation directed by aliphatic secondary amines (Scheme 15).[26a] Before this report, palladium-catalyzed carbonylative cyclization of *N*-arylamides successfully provided succinimides *via* β-C(sp^3)–H activation.[26b]
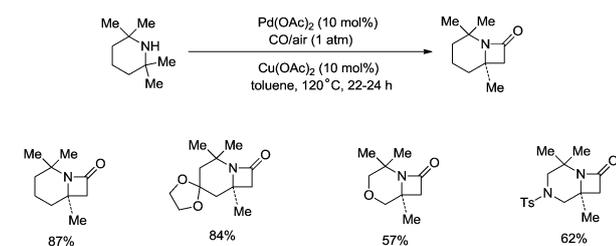
Late-stage carbonylative cyclization of an estrone derivative, amino acids and peptides *via* palladium-catalyzed γ-sp^3 C–H bond activation was achieved, affording richly functionalized γ-lactams successfully (Scheme 16).[26c] *N*-(2-pyridyl)sulfonyl (*N*-SO$_2$Py) was used as a directing group, overriding other
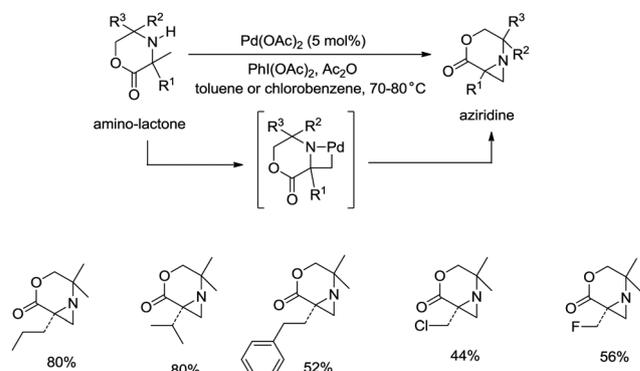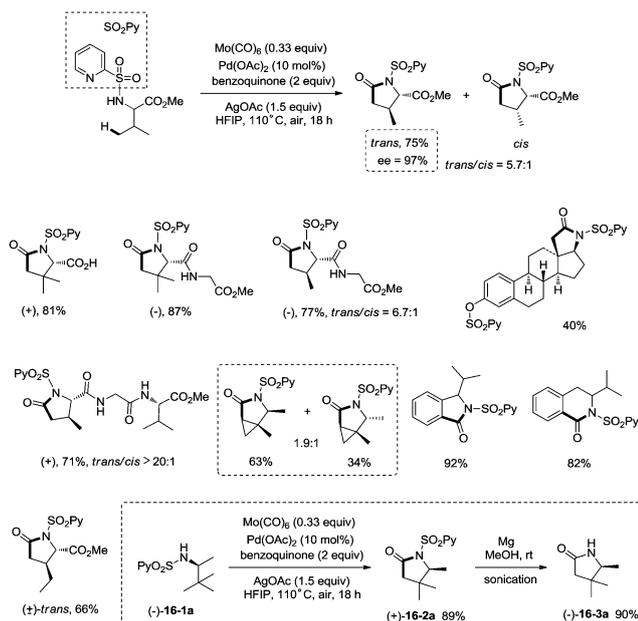

Scheme 13 Palladium-catalyzed aziridination.
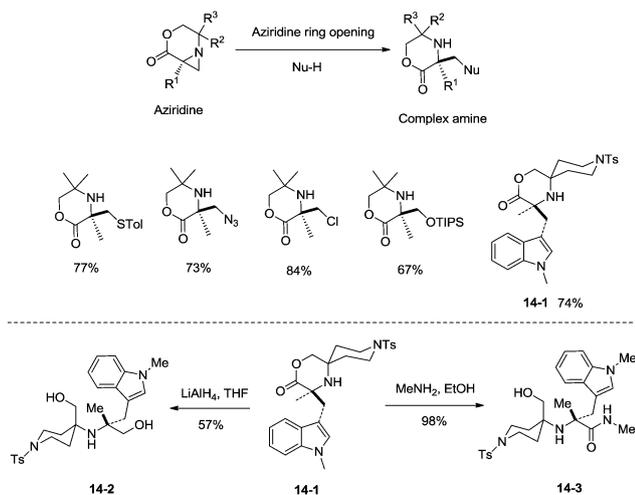
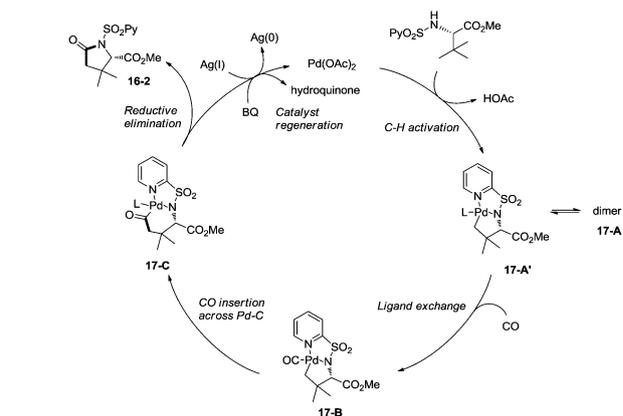**Scheme 14** Aziridine ring opening with nucleophiles.

Scheme 15 Pd-catalyzed C–H carbonylation.

Scheme 16 Carbonylative cyclization of an estrone derivative, amino acids and peptides.

inherent substrate coordinating elements. The directing auxiliary could be removed conveniently, and a free β-lactam (−)-**16-3a** was obtained in 90% yield upon treatment of (+)-**16-2a** with


**Scheme 17** The mechanism for carbonylative cyclization.

magnesium turnings at room temperature under sonication overnight. Coordination of the directing group to palladium(II) and subsequent C–H activation give the Pd(II) complex **17-A′** (Scheme 17), ligand exchange produces the intermediate **17-B**, CO insertion affords the intermediate **17-C**, reductive elimination affords the product **16-2**, and the catalyst is regenerated by oxidants (AgOAc and benzoquinone).

In 2016, a palladium acetate-catalyzed bidentate-ligand-directed synthesis of β-lactams *via* intramolecular amidation of unactivated sp^3 C–H bonds was reported by Wu and co-workers (Scheme 18),[27] the transformation proceeded smoothly in excellent yields up to 98%, and the bidentate amides derived from 8-amino quinoline were used as substrates in this transformation. This strategy can be applied to the stereoselective synthesis of diazabicyclic β-lactams (**18-2a**) with 86% yield, and 5-methoxy-quinolin-8-yl (MQ) of the directing groups and protecting group benzyloxycarbonyl (Cbz) in the target molecules can be removed readily on treatment with ceric ammonium nitrate (CAN) and hydrogen (Scheme 19). The key intermediate for the synthesis of MK-8712, *cis*-fused diazabicyclic β-lactams (−)-**19-1** was obtained from starting material L-proline.

In 2017, Wu and co-workers reported the synthesis of polycyclic azetidines and pyrrolidines also using the strategy palladium-catalyzed *N*,*N*-bidentate amide-directed intramolecular
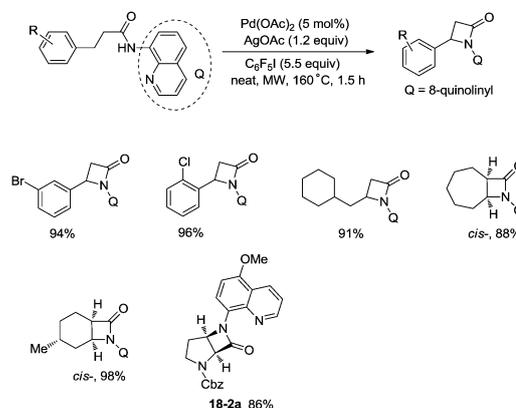

Scheme 18 Synthesis of β-lactams.
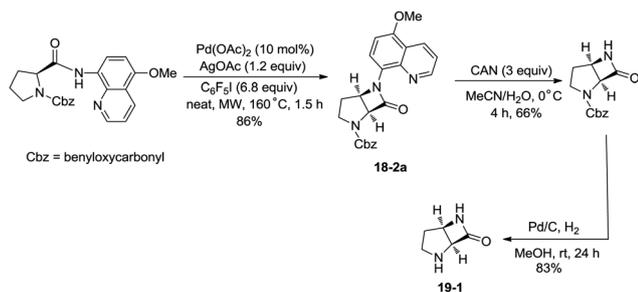
**Scheme 19** Stereoselective synthesis of diazabicyclic β-lactams.
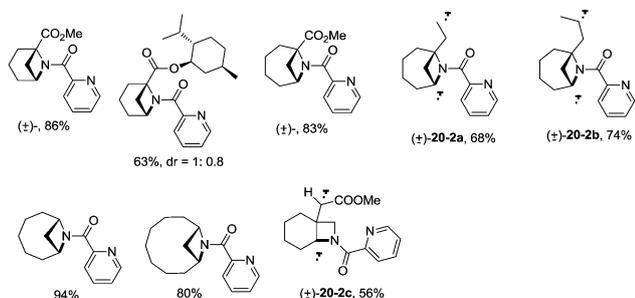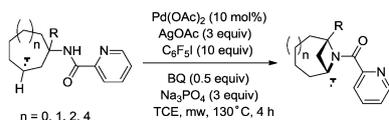
Scheme 20 Azetidines synthesis.

coupling of sp[3] C–H and N–H, but using picolinamides as the directing groups (Scheme 20).[28] The secondary γ-sp[3] C–H bonds on the ring were preferentially activated over the primary or secondary sp[3] C–H bonds on the acyclic side chain (**20-2a**, **20-2b** and **20-2c**), affording monocyclic or bicyclic azetidines effectively. When 2,6-dimethoxybenzoic acid and 1-iodo-4-nitrobenzene were used as the key additives, the intramolecular amination also occurred at the δ position, the polycyclic pyrrolidines were obtained, the highest yield is 88% (**21-1**), and the other substrates afforded a mixture of polycyclic azetidines and pyrrolidines in an approximate 1:1 ratio (Scheme 21).

Palladium-catalyzed intramolecular allylic C–H amination is a valuable access to construct nitrogen heterocyclic scaffolds.
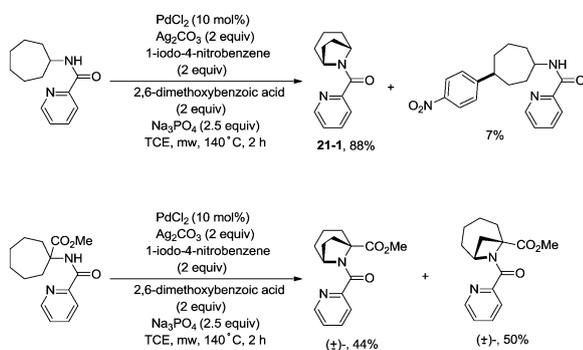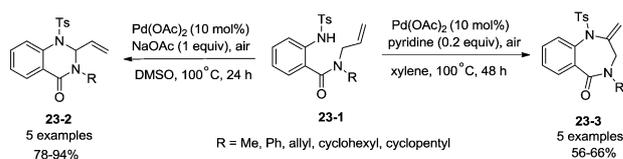

Scheme 21 Pyrrolidine synthesis.
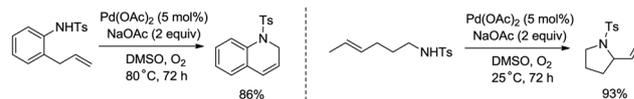

Scheme 22 C–N coupling and cyclization.

In 1996, Pd(ɪɪ)-catalyzed cyclization of olefinic tosylamides was achieved (Scheme 22).[29a] A π-allylpalladium intermediate was more likely involved than an aminopalladation intermediate in this transformation. Allylic C–H bonds were coupled with the nitrogen atom of amides, affording 2-vinylpyrrolidines, 1,2-dihydroquinolines, *etc.*

Whether a mechanism involves a η[3]-allylpalladium intermediate or an aminopalladation intermediate in intramolecular Pd-catalyzed amination of *N*-allyl-anthranilamides could be controlled by reaction conditions (Scheme 23).[29b] The mechanism involving a η[3]-allylpalladium intermediate **23-A** leads to the formation of six-membered 2-vinylquinazolin-4-ones **23-2**, and the mechanism involving an aminopalladation intermediate **23-B** leads to the formation of seven-membered 2-methylene-1,4-benzodiazepin-5-ones **23-3**.

In 2007, White and co-workers developed palladium(ɪɪ)/bis-sulfoxide-catalyzed intramolecular allylic C–H amination reaction of but-3-enyl *N*-tosyl carbamates, functionalized five-membered *anti*-oxazolidinones were provided with high diastereoselectivity, and a π-allyl Pd intermediate is involved in the transformation (Scheme 24).[29c] Useful *syn*-1,2-amino alcohols could be obtained *via* further transformation. In 2009, the same group developed a new transformation with a similar catalytic system, affording six-membered *syn*-oxazinanones from pent-4-enyl *N*-(4-nitro-phenylsulfonyl) carbamates (Scheme 24), which enables the synthesis of *syn*-1,3-amino alcohols.[29d] The reaction rate of the formation of a six-membered product was increased significantly when changing the substrate from a *N*-tosyl carbamate to a *N*-(4-nitrophenylsulfonyl) carbamate. Allylic C–H bonds of terminal olefins were selectively aminated over that of internal olefins. In the same year (2009), Poli and co-workers found that using acetic

Scheme 23 Formation of a six- or seven-membered ring.

2007:

8%, 18:1 (*anti*:*syn*)   86%, 1.6:1 (*anti*:*syn*)   84%, 7:1 (*anti*:*syn*)   84%, 1.8:1 (*anti*:*syn*)


2009:
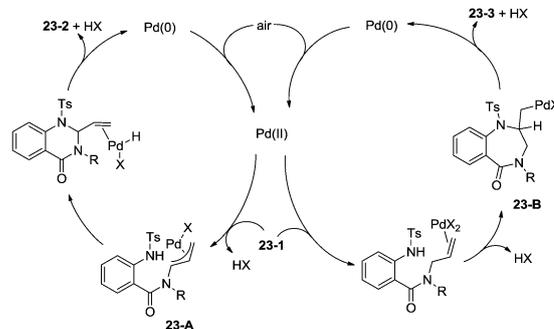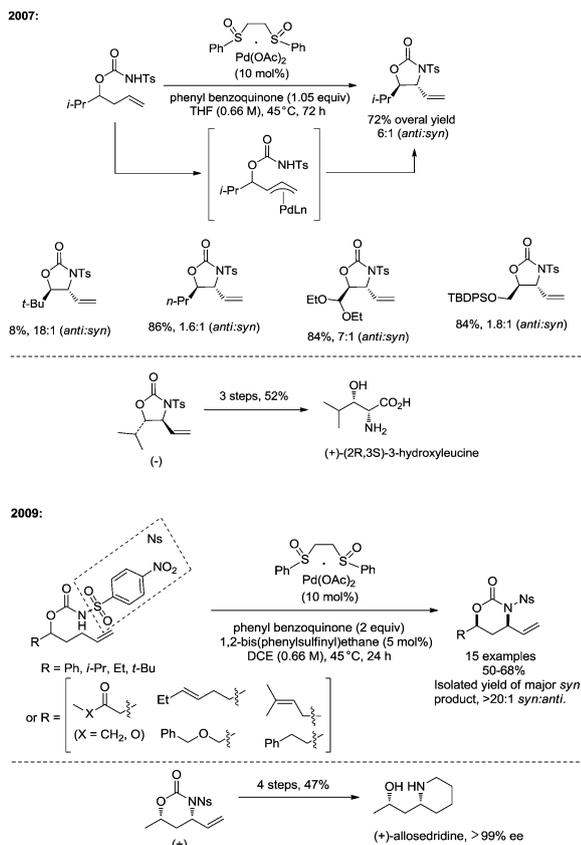
Scheme 24 Allylic C−H amination by White.

acid as solvent could significantly accelerate the Pd(ɪɪ)-catalyzed cyclization of but-3-enyl *N*-tosyl carbamates and pent-4-enyl *N*-tosyl carbamates,[29e] affording oxazolidinones and oxazinanones in high yields and with high diastereoselectivity.

Regioselectivity of Pd(ɪɪ)-catalyzed intramolecular allylic C–H amination of ω-unsaturated *N*-sulfonylamines could be modulated by a Brønsted base, which was reported by Liu and co-workers in 2009 (Scheme 25).[29f] Formation of a N–Pd bond is promoted by a Brønsted base (NaOBz), favouring the formation of intermediate **25-C**, reductive elimination gives a seven-membered
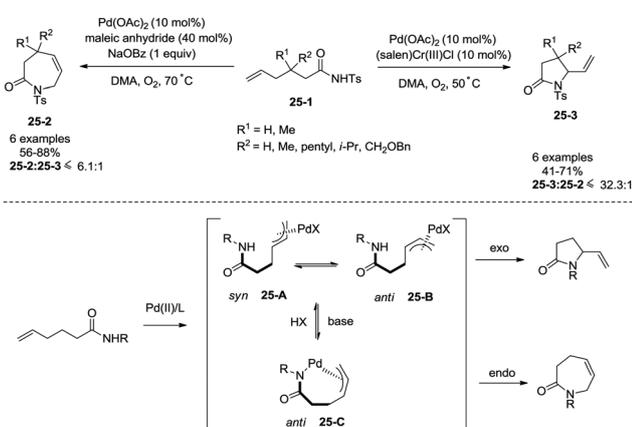
Scheme 25 Regioselectivity in intramolecular allylic amination.
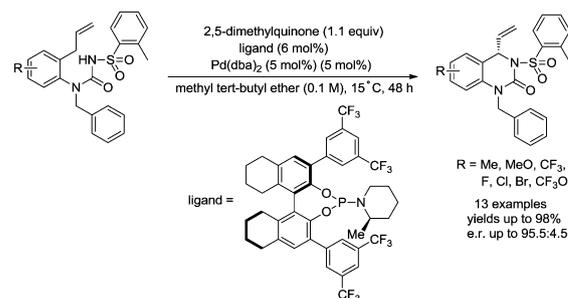
Scheme 26 Synthesis of chiral hydropyrimidinones.
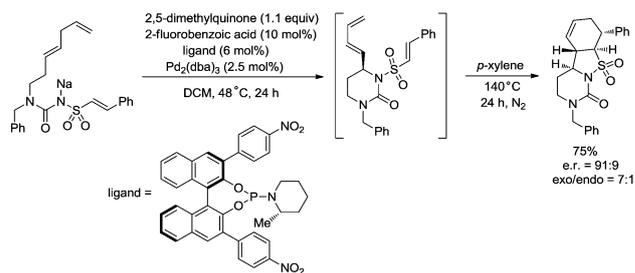
**Scheme 27** Synthesis of a chiral polycyclic heterocycle.

ring product 3,4-dihydro-1*H*-azepin-2(7*H*)-one. The intermediates **25-A** and **25-B** give a five-membered ring product 5-vinylpyrrolidin-2-one.

In 2017, Gong and co-workers reported an asymmetric C–N coupling to access chiral hydropyrimidinones *via* palladium-catalyzed allylic C–H amidation (Scheme 26),[29g] the cyclization proceeded smoothly with high yields (up to 98%), the enantio-selectivity is high when an H8-BINOL-derived phosphoramidite ligand was used, and the enantiomeric ratio is up to 95.5 : 4.5. The reaction conditions of the allylic C–H amidation cyclization were slightly modified to synthesize more complex polycyclic heterocycles (Scheme 27). A dienyl sodium *N*-sulfonyl amide bearing an arylethene-1-sulfonyl group underwent the allylic C–H amidation cyclization, and a subsequent diastereoselective intramolecular Diels–Alder reaction afforded a chiral polycyclic heterocycle in 75% overall yield, e.r. = 91 : 9, *exo*/*endo* = 7 : 1.

3. Copper catalysis

Inspired by the reports[20] on the palladium-catalyzed amino-quinoline-directed intramolecular amidation of unactivated sp^3 C–H bonds from Chen's group, Ge and co-workers developed copper(ɪ) chloride-catalyzed bidentate-ligand-directed intra-molecular amidation of sp^3 C–H bonds in 2014 (Scheme 28).[30a] This strategy provides an alternative approach to afford mono-, spiro-, and bicyclic β-lactams, important structural units in many biologically active naturally-occurring products and synthetic medicines.

This reaction preferentially occurred at the β-methyl groups rather than the β-methylene groups [(**28-2a**)–(**28-2d**)] and the γ-positions on the phenyl groups (**28-2e**). The C–H bonds of the γ- or δ-methyl group did not undergo the amidation
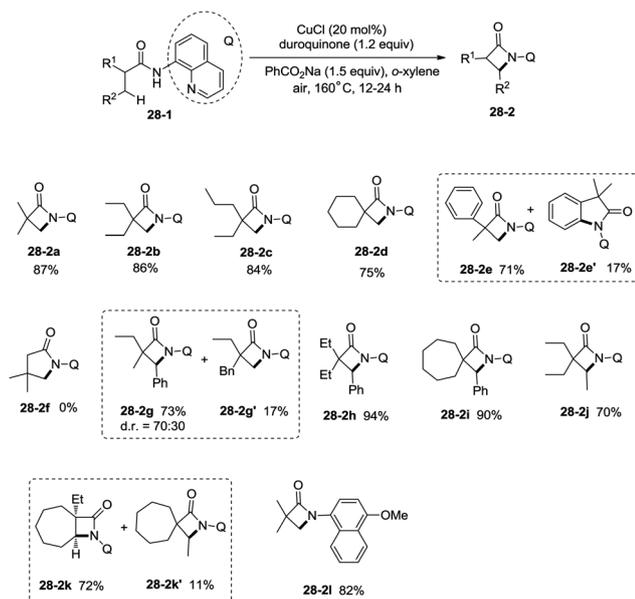
Scheme 28 Direct amidation on sp³ C–H bonds.

(**28-2b**, **28-2c**, **28-2f**), thus indicating that a five-membered ring cyclometalation intermediate is more easy to form than the six or seven-membered ring intermediate in the cyclometalation step under these reaction conditions. Secondary benzylic β-C–H bonds are preferentially amidated over the C–H bonds of the β'-methyl groups and unactivated β'-methylene groups [(**28-2g**)–(**28-2i**)], the unactivated secondary β-methylene groups are preferentially amidated over the γ-methyl groups because a five-membered ring cyclometalation intermediate is more easy to form than a six-membered ring cyclometalation intermediate (**28-2j**). Furthermore, the ring β-carbon atoms are preferentially amidated over acyclic β'-carbon atoms (**28-2k**), and the bicyclic β-lactam compound (**28-2k**) was provided with high *syn* diastereoselectivity. A tertiary α-carbon atom is necessary for this reaction.

The 5-methoxyquinolyl group of 1-(5-methoxyquinolin-8-yl)-3,3-dimethylazetidin-2-one (**28-2l**) was removed with ceric ammonium nitrate (CAN) according to the report from Chen's group,[20] and the free β-lactam product **29-1** was obtained in 63% yield, which is a useful intermediate for further manipulation (Scheme 29).

A plausible mechanism for this transformation is proposed (Scheme 30). Coordination of the substrate **28-1** to a copper(II) species and ligand exchange give the five-membered ring copper(II) complex **30-A**, and C–H activation at the β-position (cyclocupration) produces a fused two five-membered rings
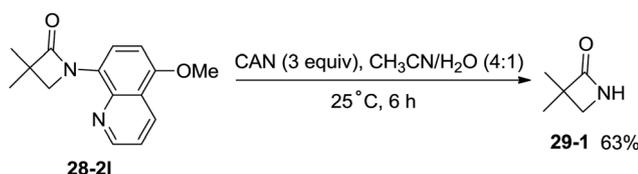
Scheme 29 Oxidative cleavage of the 5-methoxyquinolyl group.
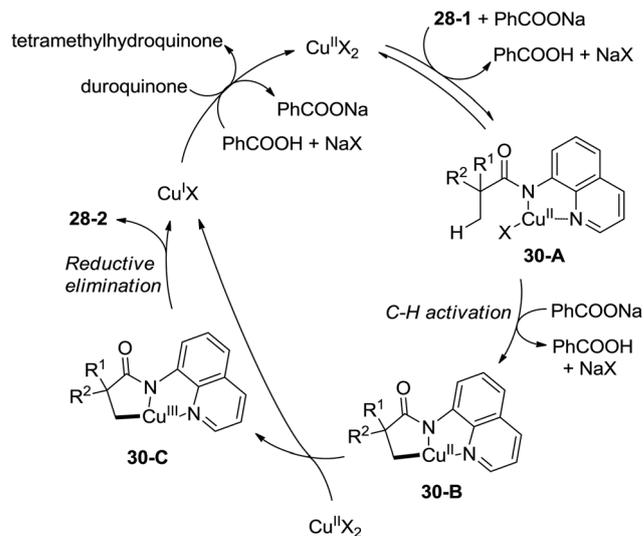
Scheme 30 Plausible reaction mechanism.

copper(II) complex **30-B**. Oxidation of **30-B** produces the copper(III) complex **30-C**, which produces the β-lactam product **28-2** *via* reductive elimination. The *in situ* formed copper(I) species is reoxidized to the copper(II) salts by duroquinone. A sequential chlorination and amidation process was also thought to be possible.

In the same year, Kanai and co-workers reported a copper(II) acetate-catalyzed intramolecular sp³ C–H amidation using a silver carbonate oxidant (Scheme 31).[30b] The reaction proceeded at the β-methyl group or benzylic position of an alkyl chain, affording β-lactams conveniently with good functional group tolerance. A Cu(III)/Cu(I) catalytic cycle was proposed for this transformation (Scheme 32).

Building upon the copper-catalyzed bidentate-ligand-directed intramolecular amidation of sp³ C–H bonds,[30] You *et al.* developed a CuI (20 mol%)-catalyzed intramolecular amidation of unactivated
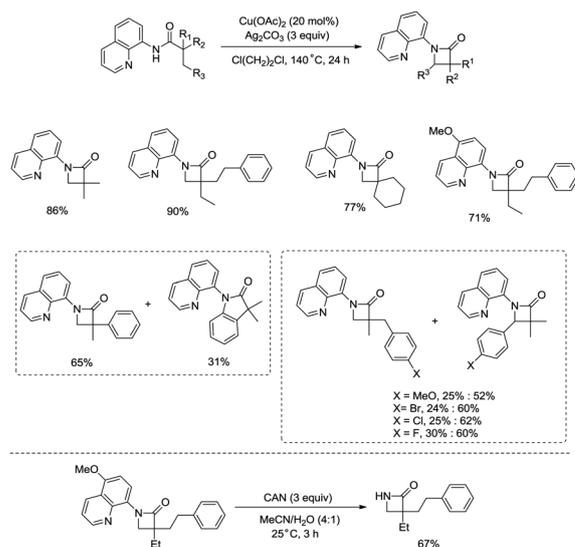
Scheme 31 Copper(II)-catalyzed cyclization by Kanai.
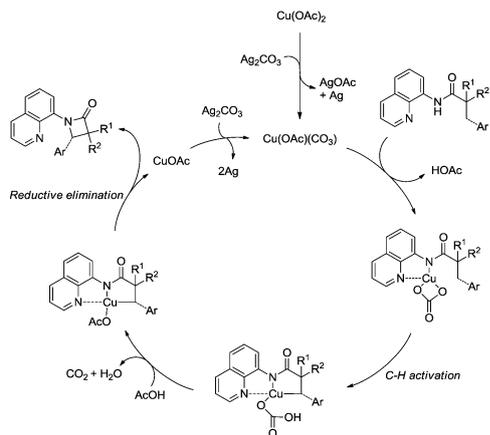
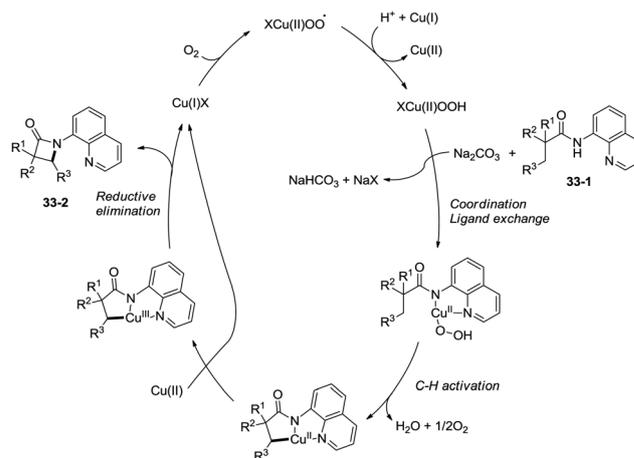**Scheme 32** The mechanism for copper(II)-catalyzed cyclization by Kanai.


Scheme 34 The mechanism using oxygen as an oxidant.

sp³ C–H bonds using oxygen as the sole oxidant. Oxygen is a cheap, non-poisonous and "green" oxidant, and the only byproduct of oxidation is water (Scheme 33).[31a] A series of aliphatic amides were transformed into the corresponding β-lactam derivatives in good to excellent yields (up to 98%). The β-methyl groups were preferentially amidated over the γ- and δ-methyl groups (**33-2a, 33-2b, 33-2c**), because the formation of a five-membered ring cyclocupration intermediate is more feasible than that of a six- or seven-membered ring intermediate in the cupration step. The C–H bonds of the β-methyl groups are preferentially amidated over the C–H bonds of the β-methylene groups including secondary β-benzylic C–H bonds (**33-2a, 33-2c, 33-2d, 33-2e, 33-2f, 33-2g**). In contrast to these results, a preference for the β-benzylic C–H bonds over the C–H bonds of the β-methyl groups was observed in the previous reports by Ge and co-workers.[30] The substrates

with cyclic chains produced two kinds of β-lactams from the amidation of both the β-methyl and the methylene, the yields of the spiro-products (**33-2h, 33-2i, 33-2j**) were slightly higher than that of the fused products (**33-2h′, 33-2i′, 33-2j′**). 2-Phenyl-substituted propanamide derivative afforded the β-lactam in 82% yield (**33-2k**) from amidation of β-methyl, and no product from amidation of phenyl was observed.

The reaction systems of the amidation used by You et al. and Ge et al.[30a] are the same, including quinolin-8-amine derived amide substrates, Cu(I) salt catalysts, oxidants and Brønsted bases, so the plausible mechanism proposed by You et al. is similar to that proposed previously by Ge and co-workers. It is worth noting that the only byproduct is water using oxygen as the oxidant (Scheme 34).[31b]

The removal of the quinolyl moiety in β-lactams needs the use of the 5-methoxy quinolyl group, and it is difficult to synthesize the 5-methoxy quinolyl derivatives due to a long synthetic route.[20,30] You et al. successfully synthesized free β-lactams by sequential Ni(acac)₂-catalyzed methoxylation, CuI-catalyzed amidation, and oxidative cleavage, and the synthetic route is shorter than the previous ones (Scheme 35).

On the basis of palladium-catalyzed isoindolone synthesis from 2,6-dimethyl-N-(8-quinolinyl)benzamides as reported by Zhang,[23] Miura and co-workers developed a copper acetate-catalyzed intramolecular benzylic C–H amidation for the synthesis of isoindolinones (Scheme 36).[32] The reaction was compatible with electron-neutral and electron-donating substituents as well as electron-withdrawing halogen functionalities, which can be
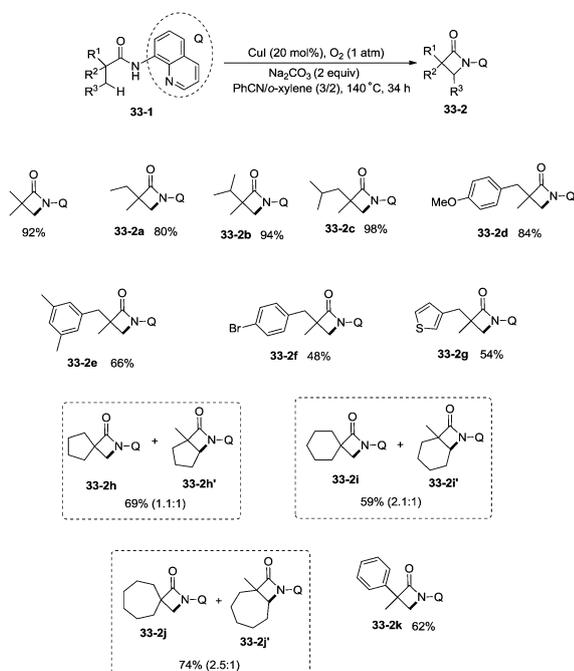
Scheme 33 Copper-catalyzed intramolecular dehydrogenative amidation.
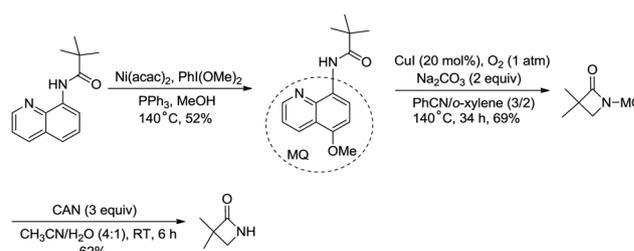
Scheme 35 Synthesis of free β-lactams.
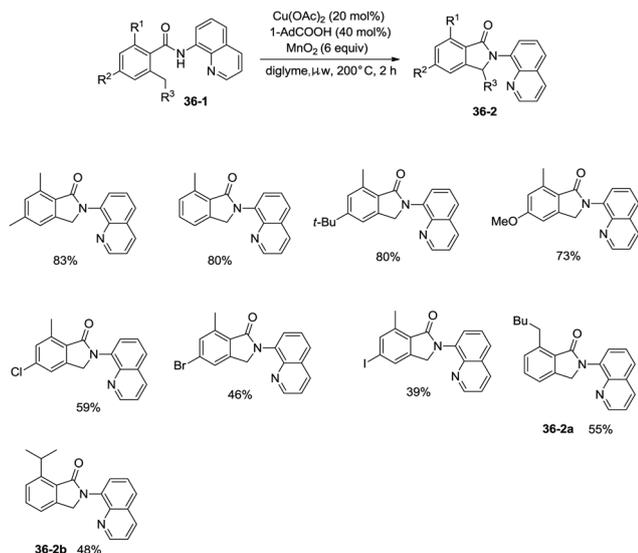
Scheme 36   Cu-catalyzed intramolecular amidation.

Scheme 37   Transformation of 2-methyl-5-substituted benzamides.

used for further coupling reactions. The amidation preferentially occurred at the *ortho* methyl over the *ortho* methylene or methyne, delivering the corresponding isoindolinones (**36-2a, 36-2b**). 2-Methyl-5-substituted benzamides could work well to give the corresponding isoindolinones under the revised conditions (Scheme 37).

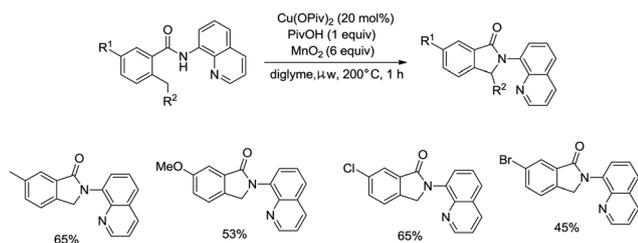Under identical conditions, the 5-methoxyquinolin-8-amine derived benzamide **38-1** also worked well to give the desired product **38-2** in 60% yield. The NH isoindolinone **38-3** was obtained in 51% yield *via* demethylation with BBr$_3$ and oxidation with PhI(TFA)$_2$ (Scheme 38).

A possible mechanism was proposed (Scheme 39). Coordination of the benzamide **36-1** with Cu(OR)$_2$ along with ligand exchange form a chelated Cu(ɪɪ) species **39-A**. Subsequent benzylic C–H
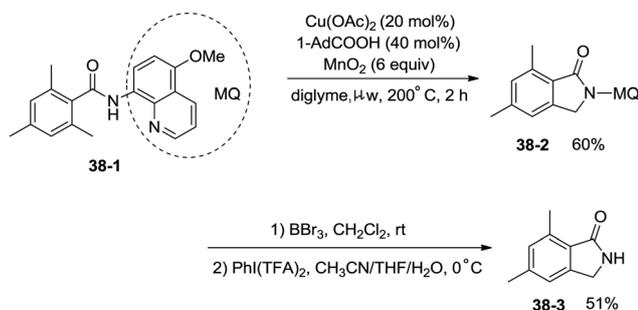

Scheme 38   Removal of MQ with BBr$_3$ etc.
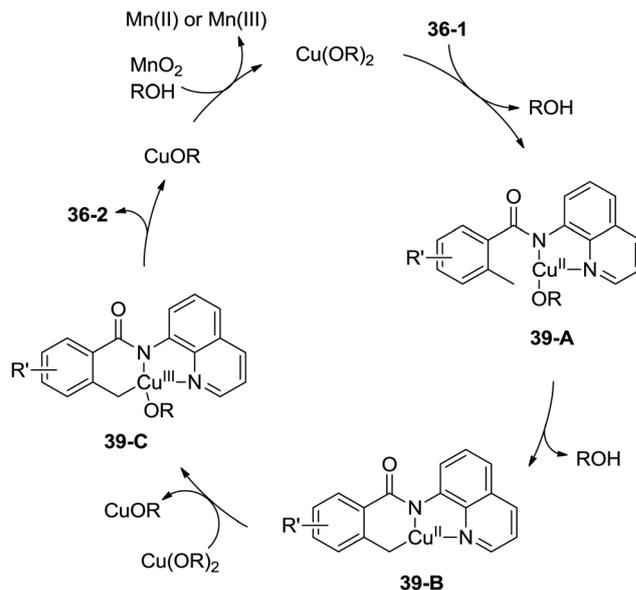
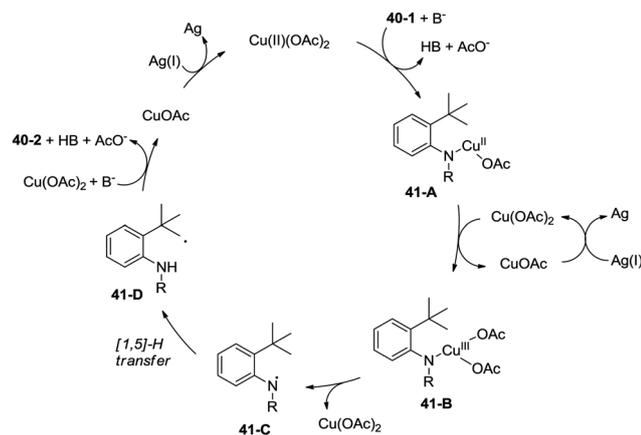Scheme 39   Mechanism for Cu-catalyzed synthesis of isoindolinones.

activation (cyclometalation) generates the fused five-membered and six-membered ring Cu(ɪɪ) complex **39-B**, which was oxidized to the Cu(ɪɪɪ) intermediate **39-C**, and then reductive elimination gives the isoindolinone **36-2**. The Cu(ɪɪ) species was regenerated *via* oxidation of the generated Cu(ɪ) species, which finishes the catalytic cycle.

Inspired by the palladium-catalyzed synthesis of indolines from anilines as reported by Glorius and co-workers,[18] Shi *et al.* developed a copper acetate-catalyzed intramolecular amidation of unactivated sp^3 C–H bonds in 2016 (Scheme 40),[33] affording *N*-substituted indolines efficiently. The substrates with different *N*-substituents could undergo the amidation (**40-2a**) smoothly, and the substrates with formyl, propionyl, isobutyryl, pivaloyl, and benzoyl substituents produced indolines in good to excellent yields. However, increase of the *N*-substituent size gradually decreased the yields. The product yield of *N*-trifluoroacetanilide was much lower probably due to the lower electronic density of the amide nitrogen. Moreover, substrates with carbamates, sulfonamides, and primary/secondary amines did not work, and the corresponding amidation/amination products were not found (**40-2b**), further implying the electronic effects of the substituents on the reaction. The reaction of acetanilides tolerated well both electron-donating and -withdrawing groups. The functionalization preference of the sp^2 C–H bonds over the sp^3 C–H bonds for the amidation was observed (**40-2c**), giving the carbazole in 82% yield. The secondary C–H bonds also worked albeit with a lower yield of 47% (**40-2d**). The secondary C–H bonds were found significantly preferable for the amidation over the primary C–H bonds (**40-2e, 40-2e'**), and the product yields ratio was 57 : 5. A notable preference for the activation of the activated position was discovered (**40-2f, 40-2g**), and the desired products were obtained in good yields (74%, 82%).

A radical mechanism was proposed for the amidation reaction (Scheme 41). Deprotonation and subsequent coordination of the amide **40-1** with Cu(OAc)$_2$ gives Cu(ɪɪ) complex **41-A**, which can be oxidized to Cu(ɪɪɪ) complex **41-B**. The Cu(ɪɪɪ) complex **38-B** forms
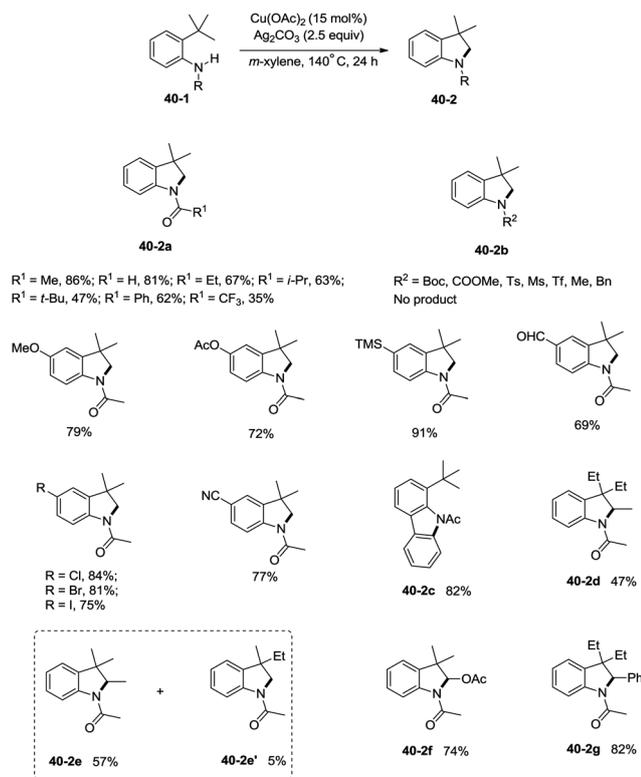
**Scheme 40** Cu-catalyzed synthesis of indolines.

Scheme 41 Plausible reaction mechanism for the Cu-catalyzed synthesis of indolines.

the nitrogen radical species **41-C**, and then a carbon radical species **41-D** was generated *via* a 1,5-hydrogen atom transfer (HAT), which usually occurs in the Hofmann–Loffler–Freytag (HLF) reaction.[34] The carbon radical **41-D** undergoes oxidation, then coupled with the amide nitrogen to form the desired product **40-2**. The Cu(ı) species is reoxidized to Cu(ıı) species by Ag$_2$CO$_3$, which completes the catalytic cycle.

4. Silver catalysis

In 2014, Shi and co-workers developed the silver acetate-catalyzed direct amination of primary sp^3 C–H, secondary benzylic C–H
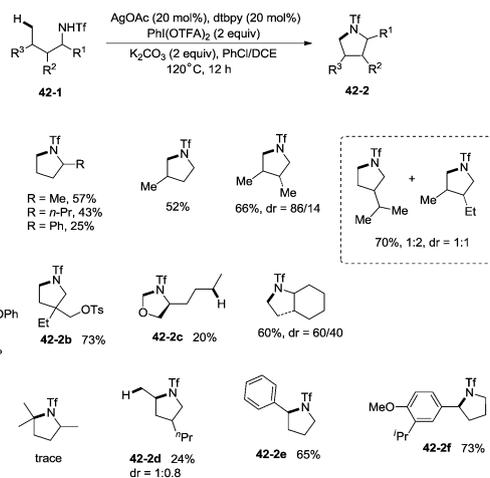
Scheme 42 Amination of primary and benzylic C–H bonds.

and aryl C–H bonds from linear triflamide (1,1,1-trifluoro-methanesulfonamide) **42-1**, providing the cyclized products **42-2** in fair to good yields (Scheme 42).[35] *O*-containing functional groups are well tolerated (**42-2a**, **42-2b**, **42-2f**), and the common leaving group -OTs (4-toluenesulfonoxyl) was also commendably compatible (**42-2b**). A 1,2-amino alcohol derivative afforded oxazolidine (**42-2c**), indicating the preference of functionalization for the C–H bonds adjacent to the heteroatom. In contrast to Hofmann–Lofler–Freytag reactions[39] or nitrene insertions,[5–8] primary C–H bonds are more reactive than secondary or tertiary C–H bonds. The five-membered ring product is preferentially obtained over a six-membered ring product although the reactivity of methyl is bigger than that of methylene (**42-2d**). Benzylic secondary C–H bonds could be functionalized well to give the cyclization products (**42-2e**, **42-2f**).

This methodology was also used to construct the structurally important tetrahydroquinoline scaffolds **43-2** from 3-arylpropyl triflamide **43-1** (Scheme 43). The sp^2 C–H bonds on the benzene ring are more favorable for the amidation over the primary sp^3
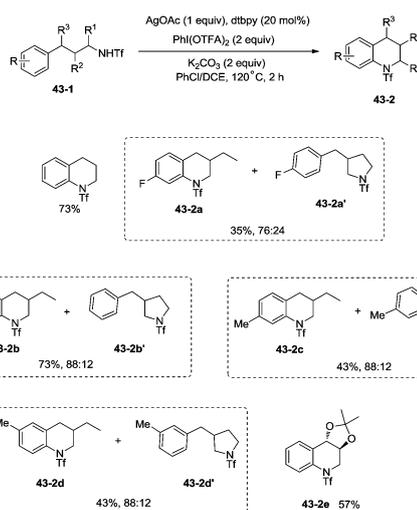
Scheme 43 Amination of aromatic C–H bonds.
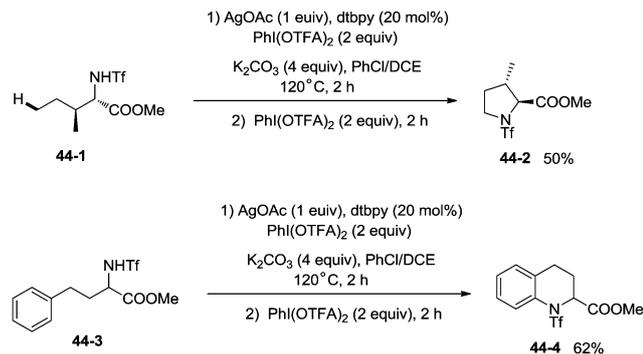
Scheme 44 Cyclization of amino acids.

Scheme 45 Synthesis of natural structures.

C–H bonds [(**43-2a**)–(**43-2d**)], and the functionalized substrate containing complex *trans*-2,2-dimethyl-1,3-dioxolane also gave the desired product in 57% yield (**43-2e**), thus indicating that the transformation tolerates well the acid-sensitive functional groups.
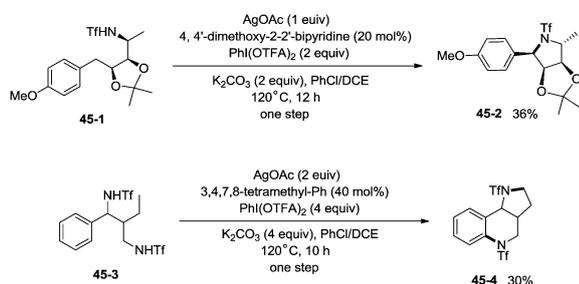
The protected linear amino acid esters **44-1** and **44-3** were transformed into 3-methylproline **44-2** and 2-tetrahydroquinonyl carboxilic ester **44-4** in acceptable yields (Scheme 44). Tetra-substituted pyrrolidine **45-2**, the epimer of natural (−)-codonopsi-nine could be obtained as a sole diastereoisomer in a single operation from the complex triflamide **45-1**. Tricyclic scaffold **45-4**, containing the core structure of the natural product (−)-martinellic acid, could also be constructed *via* primary C(sp^3)–H and aromatic C(sp^2)–H double amination in a single operation from ditriflamide **45-3**, showing the power of this chemistry in organic synthesis (Scheme 45).

A possible mechanism involving a concerted metallation/deprotonation (CMD) process was proposed (Scheme 46). Coordination of the substrate **42-1x** with silver(I) after deprotonation forms silver(I) complex **46-A**, which can be oxidized to silver(III) complex **46-B**. The activation of the primary C–H bonds gives a six-membered ring silver(III) complex **46-D**, which probably undergoes a concerted metallation/deprotonation (CMD) process (**46-C**). Reductive elimination gives the cyclization product **42-2x** along with the Ag(I) species, fulfilling the catalytic cycle.

5. Nickel catalysis

Inspired by the palladium(II)-catalyzed bidentate ligand-assisted intramolecular amidation of unactivated sp^3 C–H bonds from
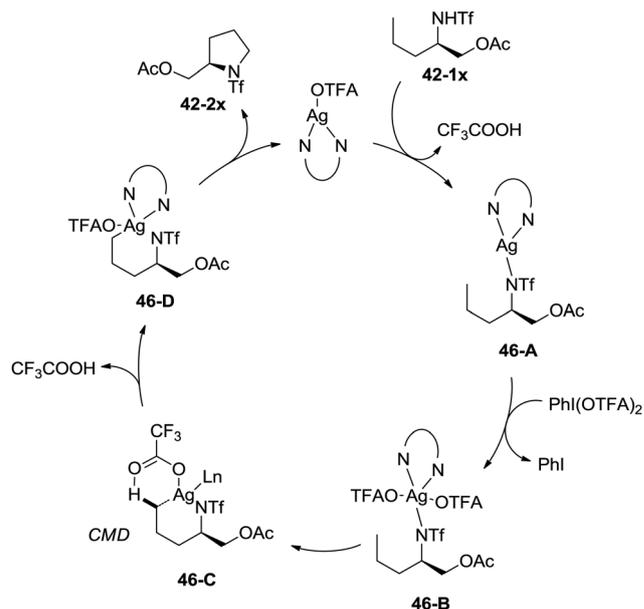
Scheme 46 Mechanism for Ag-catalyzed reactions.

Chen's group,[20] Ge and co-workers developed nickel(II)-catalyzed intramolecular cyclization on unactivated sp^3 carbon atoms in 2014 (Scheme 47).[36] The monocyclic or spiro-β-lactam derivatives were produced effectively, which are important subunits in biologically active natural products and synthetic pharmaceutical compounds. Site-selectivity is high in this reaction, and the β-methyl groups are more reactive than the β-methylene and γ-methyl groups [(**47-2a**)–(**47-2c**)]. 2,2-Disubstituted propanamides **47-1**
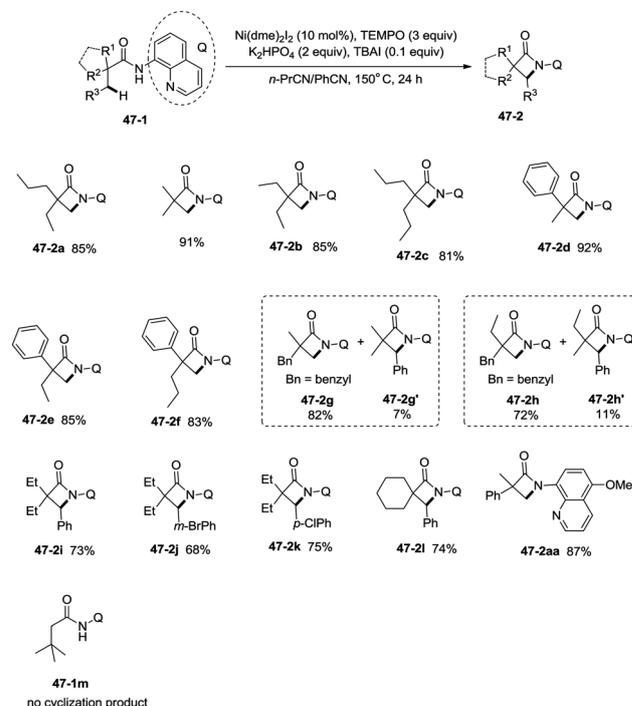
Scheme 47 Ni-catalyzed C–H amidation.
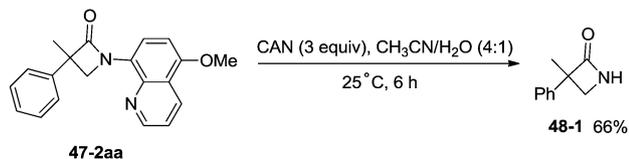
Scheme 48 Cleavage of the 5-methoxyquinolyl group.

bearing both the linear and cyclic chains were converted into the desired products **47-2** in good to excellent yields. The sp^3 C–H bonds of the β-methyl group were preferentially functionalized over the sp^2 C–H bonds of a phenyl group with the 2-phenyl-substituted substrates [(**47-2d**)–(**47-2f**)], because the generation of a five-membered ring cyclometalation intermediate is more feasible than a six-membered ring cyclometalation intermediate in the cyclonickelation step. In the previous copper-catalyzed cyclization, sp^2 C–H bonds were also amidated along with the sp^3 C–H to give two kinds of amidation products (four-membered and five-membered ring nitrogen heterocycles).[30] The primary C–H bonds of the β-methyl groups are more reactive than the secondary β-benzylic C–H bonds (**47-2g**, **47-2h**). In contrast with this, the secondary β-benzylic C–H bonds are more reactive in the previous copper-catalyzed reaction.[30] The functionalization of the benzylic secondary C–H bonds could also be effectively achieved [(**47-2i**)–(**47-2l**)]. The reaction conditions also tolerate well halogens (Cl and Br) (**47-2j**, **47-2k**). The 8-amino-5-methoxyquinoline derived substrate also undergoes the cyclization smoothly, and the yield is similar to that of the cyclization of the 8-aminoquinoline derived substrate (**47-2aa**, **47-2d**), which provides access to *N*-unprotected β-lactam derivatives.[20,30] A tertiary α-carbon atom is necessary for this cyclization, and the C–H bonds on the γ-methyl of 3,3-dimethyl-*N*-(quinolin-8-yl)butanamide **47-1m** were not amidated, which indicated that a six-membered ring intermediate is difficult to form in the cyclonickelation step under these reaction conditions.

1-(5-Methoxyquinolin-8-yl)-3-methyl-3-phenylazetidin-2-one (**47-2aa**) was subjected to the oxidative conditions for the cleavage of the auxiliary group with ceric ammonium nitrate (CAN), and the desired NH-β-lactam product 3-methyl-3-phenylazetidin-2-one (**48-1**) was produced in 66% yield (Scheme 48), which benefits further structural modification.

A plausible mechanism is proposed (Scheme 49). Coordination of the amide **47-1** to a Ni(ɪɪ) species and subsequent ligand exchange process give a chelated nickel(ɪɪ) complex **49-A**, which undergoes C–H activation affording the cyclonickelation complex **49-B**, the Ni(ɪɪɪ) species **49-C** was generated *via* the oxidation of the Ni(ɪɪ) complex **49-B**. Reductive elimination of the Ni(ɪɪɪ) complex **49-C** gives the cyclization product **47-2**. The generated Ni(ɪ) species is reoxidized to the Ni(ɪɪ) species by TEMPO, so finishing the catalytic cycle.

6. Cobalt catalysis

Inspired by the reports of transition metal (palladium, copper and nickel)-catalyzed bidentate ligand-directed sp^3 C–H functionalization processes,[20,30,36] Ge and co-workers explored cobalt
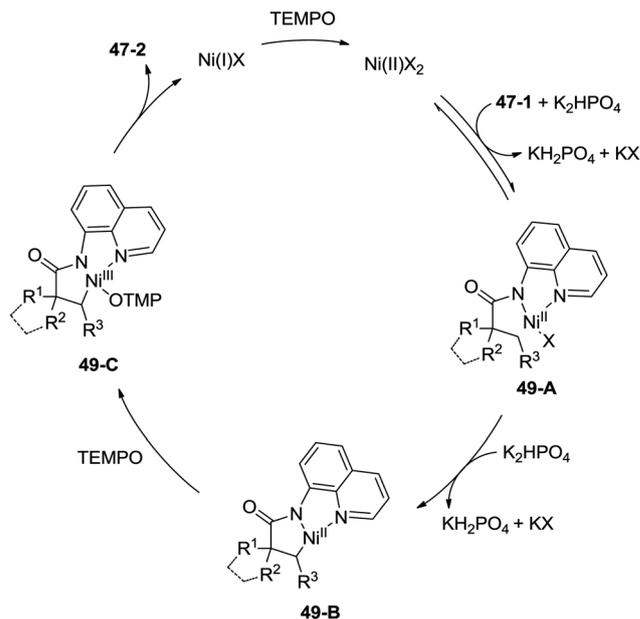
Scheme 49 Mechanism for the Ni-catalyzed amidation.

acetate-catalyzed site-selective direct sp^3 C–H functionalization with the assistance of a bidentate directing group in 2015.[37] Cobalt-catalyzed bidentate ligand-directed intramolecular cyclization of propanamides was achieved, affording β- or γ-lactams effectively (Scheme 50). This reaction proceeded with a high site-selectivity, and the C–H bonds of a β-methyl group are more favourable for the amidation than those of β-methylene and γ-methyl groups [(**50-2a**)–(**50-2e**)]. The sp^2 C–H bonds on the
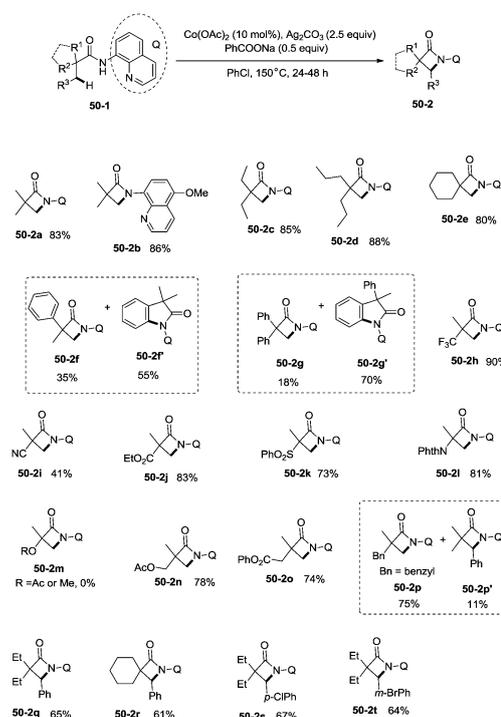
Scheme 50 Cyclization of α,α-disubstituted propanamides.

γ-positions of the benzene ring are more reactive than the sp[3] C–H bonds of β-methyl, affording the corresponding indolin-2-one derivatives as the major products (**50-2f′**, **50-2g′**). The quinolyl group and 5-methoxyquinolyl group derived substrates yielded similar results, and the cyclization yields were 83% and 86% respectively (**50-2a**, **50-2b**). The method for the removal of 5-methoxyquinolyl moiety of β- or γ-lactams has been well established.[20,30,35] Substrates with a trifluoromethyl, cyano, ethoxycarbonyl, sulfonyl or phthalimidyl group on the α-carbons were cyclized successfully [(**50-2h**)–(**50-2l**)], giving β-lactams in yields up to 90%. While substrates with α-methoxy and acetoxy groups could not be cyclized to provide the desired β-lactams (**50-2m**), β-acetoxy or phenyloxycarbonyl group substituted substrates could be cyclized to produce β-lactams **50-2n** and **50-2o** in good yields (78%, 74%). The C–H bonds of the β-methyl are more reactive than that of the β-benzyl group (**50-2p**). The β-benzylic sp[3] C–H bonds could also be cyclized to give the desired β-lactams in good yields [(**50-2q**)–(**50-2t**)]. α-Bulky group substituted substrates underwent the reaction smoothly [(**51-2a**)-(**51-2g**)] (Scheme 51). β-Phenyl substituted substrates underwent the cyclization with excellent diastereoselectivity (dr > 20 : 1) [(**51-2e**)–(**51-2g**)]. The cyclization much more favored γ-benzylic C–H bonds over the C–H bonds of the β-methyl (Scheme 52), and the major products were γ-lactams [(**52-2a**)–(**52-2c**)]. However, α-monosubstituted substrates could not be cyclized to afford the desired γ-lactams (**52-2d**, **52-2e**).

A new two-step method was developed for the removal of the quinolyl group of the lactams (Scheme 53). A methoxy group was introduced on the C5 position of the quinolyl group, and the newly generated 5-methoxyquinolyl moiety could be cleavaged with ammonium cerium(ɪᴠ) nitrate (CAN). Some free α-mono and α,α-di-substituted β-lactams, and α,α-di-substituted γ-lactams (**53-1**, **53-2**) were produced efficiently using this new method.

A possible mechanism for the formation of β-lactams was proposed (Scheme 54). Coordination of the amide **50-1** with a cobalt(ɪɪɪ) species and a subsequent ligand exchange process generate the Co(ɪɪɪ) complex **54-A**. β-C–H activation (cyclo-metalation) gives the cyclic cobalt(ɪɪɪ) complex **54-B**, which is oxidized to the Co(ɪᴠ) complex **54-C**, reductive elimination
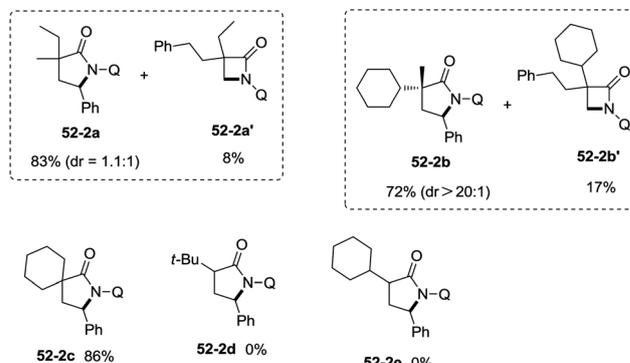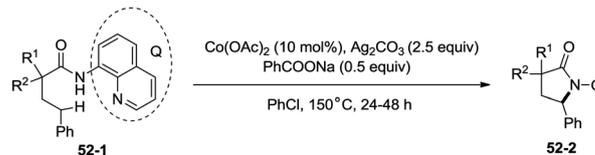
Scheme 52   Co-catalyzed synthesis of γ-lactams.
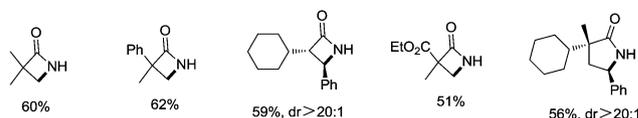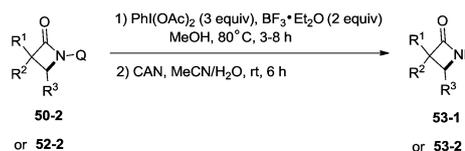
Scheme 53   The two-step removal of the quinolyl group.

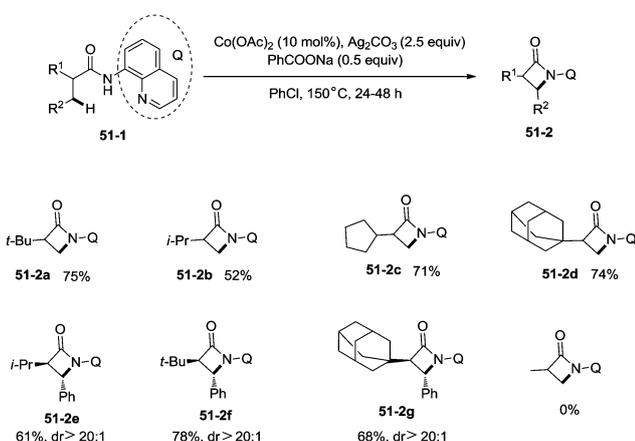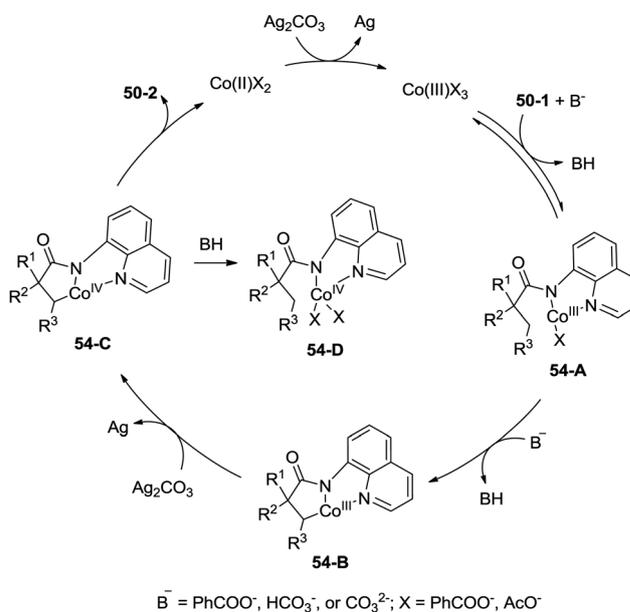Scheme 51   Cyclization of α-monosubstituted propanamides.


Scheme 54   Mechanism for cobalt-catalyzed reactions.

affords the β-lactam **50-2**. A mechanism involving the Co(ɪɪ)/Co(ɪᴠ) catalytic cycle is thought to be possible. The protonated

Co(IV) species **54-D** is possibly formed. It is thought that the mechanisms involving a radical or cationic species are possible in the formation of γ-lactam derivatives, because the γ-benzylic C–H bonds are preferentially functionalized over the β-methyl C–H bonds.

7. Ruthenium catalysis

In 2011, a ruthenium-catalyzed carbonylative cyclization of sp^3 C–H was reported, affording a series of 1-(pyridin-2-ylmethyl)-pyrrolidine-2,5-diones successfully with good functional group tolerance (Scheme 55).[38] In general, the cyclization proceeded selectively at β-methyl over methylene. A possible mechanism was proposed (Scheme 56). Coordination of the amide **55-1** to Ru and subsequent N–H activation produce the ruthenium hydride complex **56-A**, insertion of ethylene gives the ruthenium complex **56-B**, C–H activation forms the complex **56-C**, insertion of CO produces the complex **56-D**, and reductive
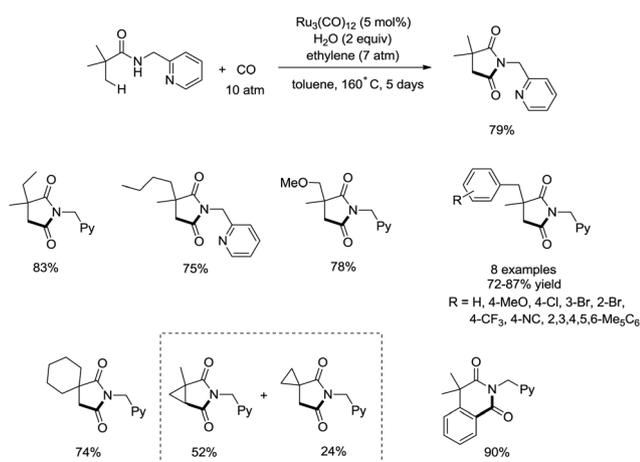
Scheme 55 Ruthenium-catalyzed carbonylative cyclization.
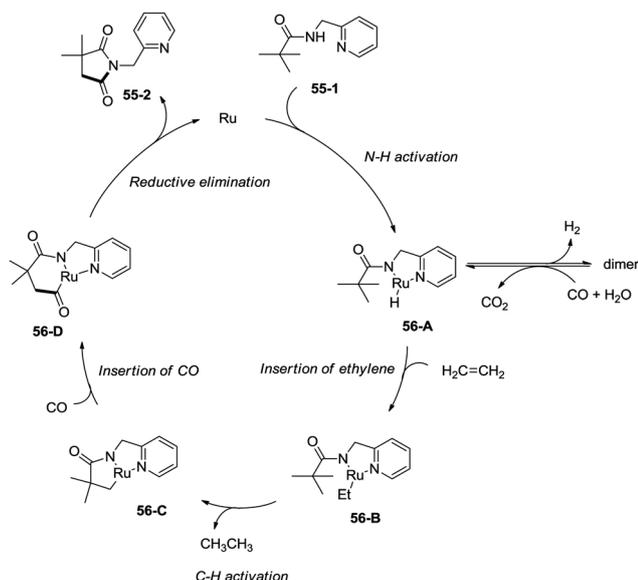
Scheme 56 The mechanism for Ru-catalyzed cyclization.
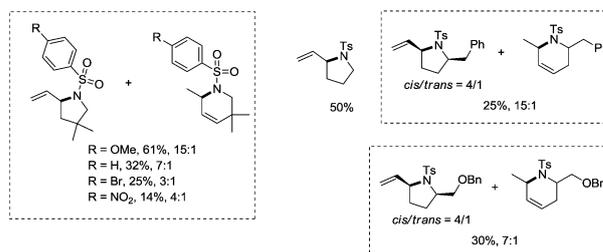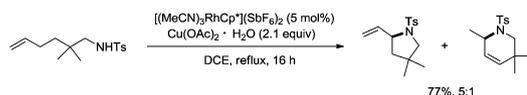
Scheme 57 Rh-catalyzed cyclization.
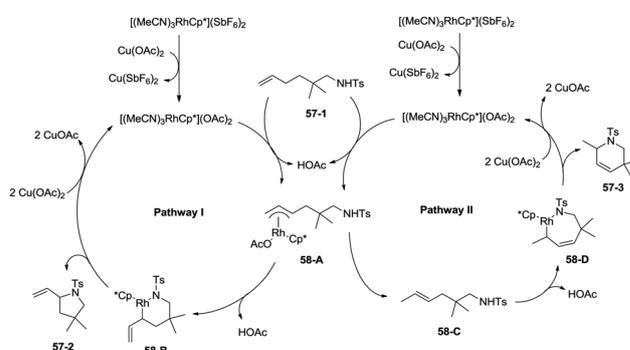
Scheme 58 The mechanism for Rh-catalyzed cyclization.

elimination gives the product **55-2**, along with the regeneration of the catalyst.

8. Rhodium catalysis

In 2012, a rhodium(III)-catalyzed intramolecular allylic C–H bond amination was developed by Cossy and co-workers, and pyrrolidines and tetrahydropyridines were synthesized in moderate to good yields from ω-unsaturated N-sulfonylamines (Scheme 57).[39] Allylic C–H bonds were selectively aminated, and aromatic, benzylic and ethereal C–H bonds did not undergo the amination. The formation of tetrahydropyridines and pyrrolidines from ω-unsaturated N-tosylamides was thought to have been achieved in two pathways (Scheme 58). A π-allylic rhodium complex **58-A** can be formed *via* C–H activation, deprotonation and coordination of the amide to Rh generate the complex **58-B** (pathway I), and reductive elimination gives the pyrrolidine **57-2**. The formation of the tetrahydropyridine **57-3** can be explained by pathway II. The isomeric olefin **58-C** is produced after the migration of a hydrogen, a π-allylic rhodium complex can be formed from **58-C** and N-metalation produces **58-D**, and reductive elimination gives the tetrahydropyridine **57-3**.

9. Conclusions and outlook

To date, a wide variety of heterocyclic scaffolds have been constructed by the strategy where a transition metal catalyzes

sp³ C–H activation and intramolecular C–N coupling. Palladium, copper, silver, nickel, cobalt, ruthenium and rhodium catalysis have been applied successfully to these transformations, and these methods complement each other. Palladium catalysis is effective for direct intramolecular sp³ C–N coupling and carbonylative cyclization. Primary C–H bonds of a methyl group, secondary benzylic or allylic C–H bonds and secondary C–H bonds of a methylene group could be activated by palladium catalysts and undergo cyclization. Three-, four-, five-, six- and seven-membered products are all likely to be produced, and the regioselectivity depends on the reaction conditions and the substrate structure. Copper catalysis is effective for direct intramolecular sp³ C–N coupling. Primary C–H bonds of a methyl group, primary or secondary benzylic C–H bonds and sp³ C–H bonds of a methylene group could be activated and undergo cyclization under Cu catalysis. Four- and five-membered products can be formed; the four-membered products are preferentially formed over the five- or six-membered products. Silver catalysis is effective for direct intramolecular sp³ C–N coupling. Primary C–H bonds of a methyl group, and secondary C–H bonds of a methylene group could be activated and undergo cycliztion. Five-membered products are preferentially produced over six-membered products in the absence of reactive sp² C–H bonds in substrates. Nickel catalysis is effective for direct intramolecular sp³ C–N coupling. Primary C–H bonds of a methyl group, and secondary benzylic C–H bonds could be activated and undergo cyclization. Four-membered products are preferentially produced over five- or six-membered products. Cobalt catalysis is effective for direct intramolecular sp³ C–N coupling. Primary C–H bonds of a methyl group, and secondary benzylic C–H bonds could be activated and undergo cyclization. Four- and five-membered products are likely to be produced, and the regioselectivity depends on the substrate structure. Ruthenium catalysis is effective for carbonylative cyclization, and primary C–H bonds of a methyl group and secondary C–H bonds of a methylene group could be activated and undergo cyclization. Five-membered products are preferentially produced over six-membered products in the absence of reactive sp² C–H bonds in the substrates. Rhodium catalysis is effective for intramolecular allylic C–H bond amination, and benzylic and ethereal C–H bonds don't undergo the amination. Five- and six-membered products could be formed, and the cyclization favours the formation of five-membered products over six-membered products.

The catalytic systems of these reactions all include catalysts and stoichiometric oxidants, and some oxidants are toxic or expensive, so improvements are needed to overcome the disadvantages existing in this area. Certain development trends of this strategy are as follows. (1) A merged photoredox and palladium-catalyzed process has been used for the synthesis of carbazoles *via* the intramolecular amination of sp² C–H bonds; the terminal oxidant is oxygen, and no stoichiometric toxic oxidant is required,[40] thus the combination of visible light photoredox and transition metal catalysis could be developed for intramolecular sp³ C–H amination. (2) Recently, regioselective electrochemical synthesis of N-heteroaromatics *via* intramolecular sp² C–H/N–H cross-coupling was reported,[41] requiring no

metal catalysts, oxidizing agents, or salt additives. Electrochemical synthesis was also applied to the intramolecular amination of sp³ C–H bonds without metal catalyst and oxidant, affording pyrrolidines, oxazolines[42] and isoindolinones,[43] so electrochemistry could be introduced further into the sp³ C–H functionalization due to its green chemistry features, and merging electrochemistry with transition metal catalysis could provide more types of heterocyclic compounds. (3) Compared with palladium, nickel and cobalt are cheaper, but reports involving Ni and Co catalysis for intramolecular sp³ C–H amination/amidation are relatively rare, so Ni and Co catalysis could be employed more for this kind of sp³ C–H cyclization. (4) Chiral heterocyclic compounds are of great medicinal importance, so asymmetric intramolecular sp³ C–H amination/amidation could be developed further in the future. (5) The most common directing groups are amides, and free amines are rarely used as a directing group for sp³ C–H cyclization. The relationship between the basicity of directing nucleophilic nitrogen sources and C–H activation reactivity is worth investigating. It would be interesting to test other nitrogen sources (carbamates, hydrazones, oximes, *etc.*) as a directing group. (6) The bidentate directing groups could promote sp³ C–H activation, but some auxiliarys could not be removed, so development of better bidentate directing groups with removable auxiliarys would be desirable.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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