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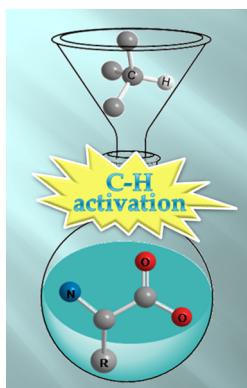
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C–H Functionalization in the Synthesis of Amino Acids and Peptides

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1. INTRODUCTION

In recent years, the pharmaceutical market has experienced a paradigm shift; as small molecules had long been thought of as the ultimate therapeutics, the use of biologics (peptides, proteins, as well as monoclonal antibodies) is now experiencing a real breakthrough. Not only is the focus on the development of new therapeutics turning toward biologics, with more biologic-based compounds being approved by the Food and Drug Administration (FDA) every year, peptides and proteins are also essential for proteomics, diagnosis, and drug delivery.¹

While natural peptides and proteins are of great importance in present day drug discovery programs, the interest in biologics containing nonproteinogenic amino acids or non-natural linkages has increased dramatically. Such compounds frequently exhibit enhanced activities and result in improved pharmacokinetic properties when compared to their natural counterparts.²

In addition to being the subunit of peptides and proteins, amino acids are employed in total synthesis and ligand elaboration as chiral building blocks, chiral ligands, or chiral catalysts.³ Because of their broad spectrum of applications and the limited number of amino acids genetically encoded, there is an urgent need for the development of new methodologies for the straightforward chemical modifications of amino acids and peptides.

Numerous strategies have been used for the synthesis of nonproteinogenic amino acids.⁴ The asymmetric Strecker reaction,⁵ the enantioselective hydrogenation of dehydroamino acid precursors,⁶ as well as the asymmetric alkylation of glycine (Gly) derivatives employing chiral auxiliaries⁷ or chiral phase-transfer catalysts⁸ have proven especially useful for the introduction of the chiral center. Other approaches consisting of the functionalization of the amino acids' side-chains, therefore taking advantage of the existing chirality, have also been extensively employed.⁹ Notably, the metal-catalyzed cross-coupling reactions to form new C–C,¹⁰ C–N, and C–O bonds have been widely applied to the synthesis of novel amino acids. The derivatization of amino acids prior to peptide synthesis but also the more challenging site-specific functionalization of peptides as well as the side-chain to side-chain peptide macrocyclization were achieved using traditional transition metal-catalyzed reactions.¹¹

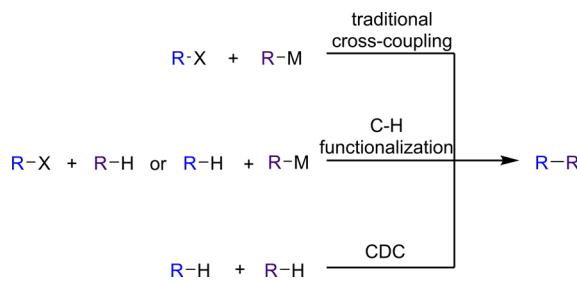
Although traditional cross-coupling reactions have revolutionized modern organic chemistry, the need for prefunctional-

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alized starting materials has prompted chemists to investigate more atom and step economic alternatives. C–H functionalization has recently emerged as a powerful tool allowing the transformation of otherwise unreactive C–H bonds, thus decreasing the amount of stoichiometric metallic waste.¹² Early examples of metal-catalyzed C–H activation were reported in the late 1960s. Notably, Fujiwara and Moritani¹³ described the C–H alkenylation of benzene with styrene in 1967, while Shilov¹⁴ published the hydrogen–deuterium exchange within C–H bonds of alkanes catalyzed by platinum salts in 1969. However, it was not until the 1980s, thanks to the respective contributions of the Bergman¹⁵ and Graham¹⁶ groups who first observed the direct oxidative addition of saturated alkanes onto iridium complexes, that the field really came alive. C–H functionalization of C(sp)–H, C(sp²)–H, and C(sp³)–H to form C–C, C–N, C–O, C–X, C–S, and C–B¹⁷ bonds has now been documented. Although the most common technique to achieve C–H functionalization involves the formation of organometallic intermediates, complementary approaches involving carbenoid and ionic intermediates are gaining considerable importance. Furthermore, the ultimate challenge to construct C–C bonds by oxidizing two C–H bonds is no longer elusive, and “catalytic dehydrogenative cross-coupling” (CDC) is now being efficiently tackled.¹⁸ Scheme 1 illustrates the evolution in the strategies employed to effect the formation of C–C/C–heteroatom bonds.

Scheme 1. Strategies for C–C/C–Heteroatom Bond Formation



C–H functionalization has, therefore, become the methodology of choice for the transformation of numerous organic molecules.¹⁹ Following our ongoing effort aimed at designing peptidomimetic libraries, we turned to the development of new methodologies to further extend the range of non-proteinogenic amino acids available as a means to increase the structural diversity of the peptides under investigation. With the upsurge of C–H functionalization protocols, we are now interested in the use of C–H functionalization as a more efficient and greener approach to fulfill our goal. In this review, we survey the progress achieved in the synthesis of amino acids and peptides using C–H functionalization techniques. This account aims to cover all of the transformations that fall under the now broad appellation that is “C–H functionalization” and does not limit itself to cross-couplings occurring through metallacycle formation. This review will be organized on the basis of the reactions’ proposed mechanisms, type of bonds functionalized, and type of bonds being formed. The general aspects of each type of C–H functionalization, including remaining challenges as well as mechanistic details, will be discussed. Thus, we hope to provide the reader with a good understanding of the state of knowledge in the field, prior to focusing on the practical

applications of C–H functionalization in the synthesis of amino acids and peptides.

2. C–H FUNCTIONALIZATION VIA ORGANOMETALLIC INTERMEDIATES

2.1. Background

The abundant literature on C–H functionalization via organometallic intermediates offers a great variety in the choice of transition metal catalysts. Although palladium remains the most versatile catalyst, reactions catalyzed by ruthenium, rhodium, platinum, nickel, and iridium have also been described.²⁰ The use of copper and iron as inexpensive and abundant metals for C–H functionalization is also slowly gaining popularity.²¹ However, unlike traditional metal-catalyzed cross-coupling reactions, C–H functionalization protocols still require relatively high catalyst loadings.

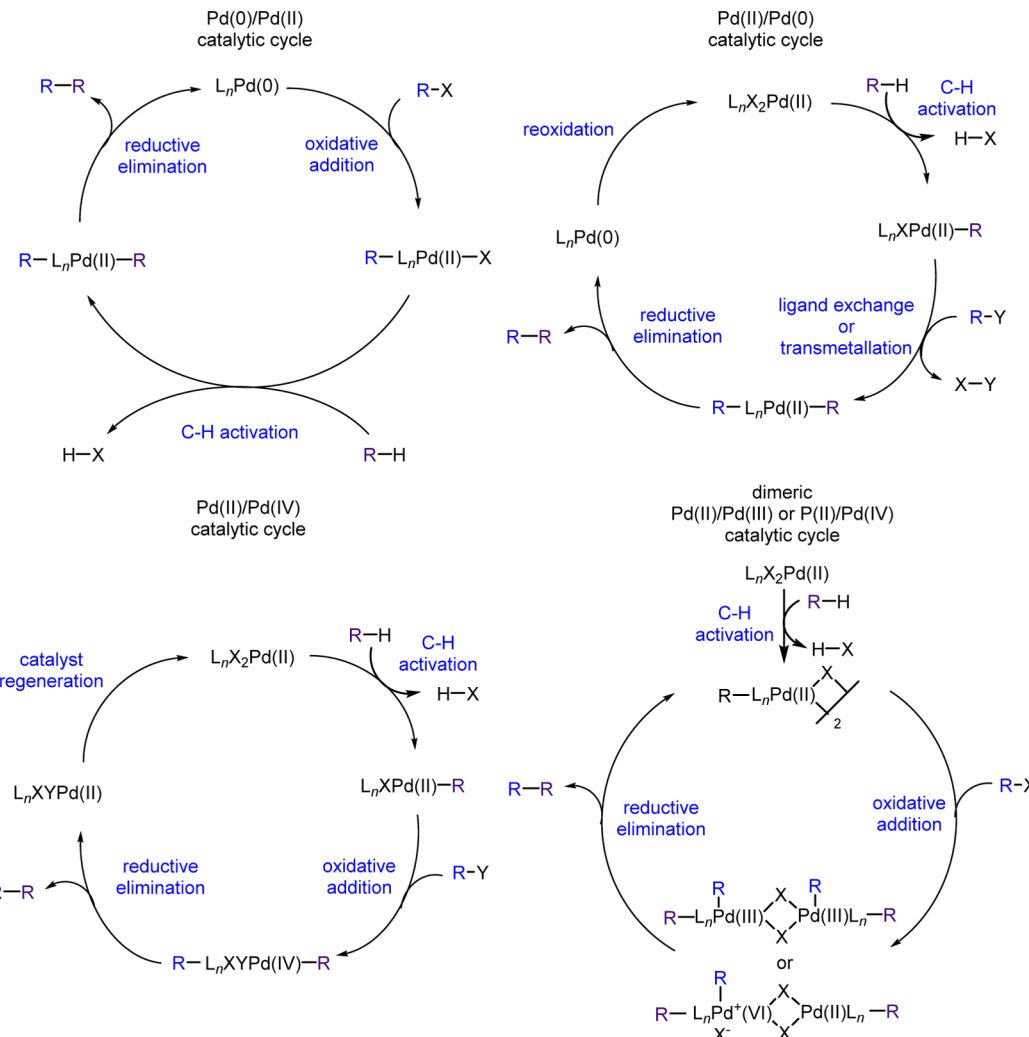
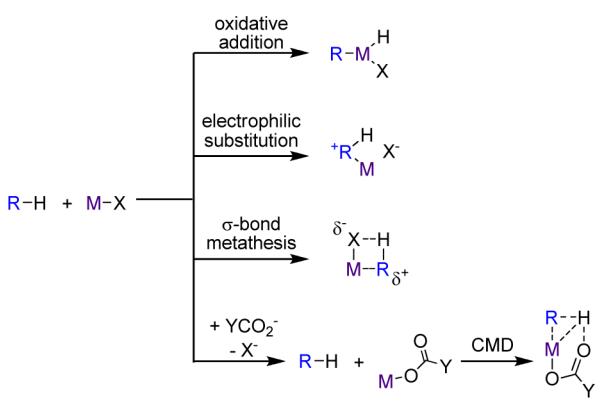
Despite the promising advances in the field of C–H functionalization, two major constraints remain. First, the necessity to overcome the relative inertness of C–H bonds has mainly limited the reaction in terms of substrate scope. Thus, the majority of work on C–H functionalization focuses on C(sp²)–H bonds in (hetero)aryl ring and acidic C(sp³)–H bonds α to electron-withdrawing groups (EWG).^{17d,22} Although activation of “unactivated” C(sp³)–H bonds, other than benzylic and α to heteroatoms, has proven a challenging task, considerable progress has been achieved thanks to the effort of multiple research groups as highlighted in several recent reviews.^{17c,23}

The second limitation comes from the inherent difficulty in differentiating the diverse C–H bonds present in a complex substrate. Site-selective C–H activation has nonetheless been accomplished through the use of directing groups (DG),²⁴ and is also rendered possible in substrates in which a prior oxidative addition step induces the metallation of a proximal C–H bond. Furthermore, nondirected C–H activation has also been carried out and affords excellent regioselectivity for various types of substrates. These nondirected C–H activations can be dictated by the nucleophilicity or the acidity of the C–H bond as well as by steric factors.

2.2. Mechanistic Studies

As mentioned previously, C–H functionalization reactions via organometallic intermediates catalyzed by palladium represent the forefront of the field and have therefore been the most extensively studied. They can be classified following the change of oxidation state occurring during the catalytic cycle (Scheme 2). C–H functionalization reactions can proceed through the well-known Pd(0)/Pd(II) catalytic cycle; however, in contrast to traditional cross-coupling reactions, C–H functionalization reactions have also been shown to follow Pd(II)/Pd(0) and Pd(II)/Pd(IV) modes of catalysis.²⁵ Furthermore, mechanistic investigations by the Sanford²⁶ and Ritter²⁷ groups suggested a plausible bimetallic palladium intermediate instead of the monometallic active palladium species commonly proposed.

Alternative mechanisms to the four highlighted above, as well as mechanisms involving different transition metals, have also been reported and will be discussed where appropriate. The C–H activation step itself has also been thoroughly investigated and is still the subject of much discussion. The principal proposed mechanisms for C–H bond cleavage; oxidative addition, σ -bond metathesis, electrophilic substitution, and concerted metallation-deprotonation (CMD); are depicted in Scheme 3.²⁸ The simultaneous metallation and intramolecular

Scheme 2. Four of the Most Common Catalytic Cycles of Palladium-Catalyzed C–H Functionalization Reactions**Scheme 3.** Principal Proposed Mechanisms for the C–H Insertion Step

deprotonation steps, first coined CMD by Fagnou and co-workers, have greatly participated to explain the regioselectivity observed for the C–H functionalization of numbers of substrates.²⁹ Furthermore, the discovery of the CMD mechanism has shed some light on the critical role of the carboxylate anion coordinated to the metal center and rationalized the use of a catalytic amount of acid such as pivalic acid as a proton shuttle between the substrate and a

stoichiometric base (e.g., K₂CO₃).³⁰ The understanding brought by the suggested CMD mechanism has catalyzed most of the recent breakthroughs in the C–H activation field.

Thanks to these mechanistic studies, organometallic chemists have gained understanding of the multitude of mechanistic considerations governing the different C–H activation/coupling catalytic cycles and are already able to better address many of the challenges posed by C–H functionalization.

2.3. C–H Functionalization in Amino Acids and Peptides

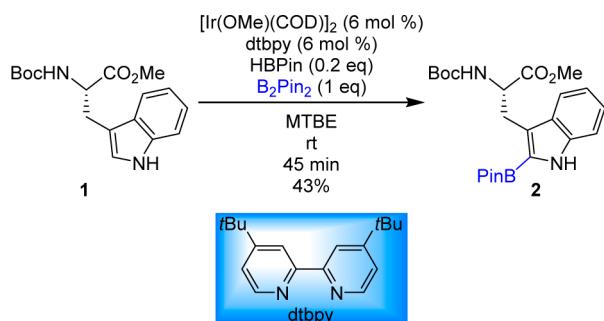
Amino acids are an important class of compounds and have therefore often been used as the benchmark for the development of new reactions; C–H functionalization is no exception. It is therefore not surprising to find amino acid substrates in reports covering almost all of the aspects of C–H functionalization.

2.3.1. Functionalization of C(sp²)–H Bonds. Often found to be crucial for the biological activity of the molecules they are part of, phenylalanine (Phe), tyrosine (Tyr), tryptophan (Trp), and histidine (His) hold a special place among amino acids. Because of the importance of these compounds for medicinal chemistry and thanks to their aromatic nature, they represent the perfect substrates for the application of C–H functionalization protocols. Reports by several groups on metal-catalyzed borylation, acetoxylation,

halogenation, and arylation reactions of aromatic amino acids have been published in recent years, which will be discussed herein.

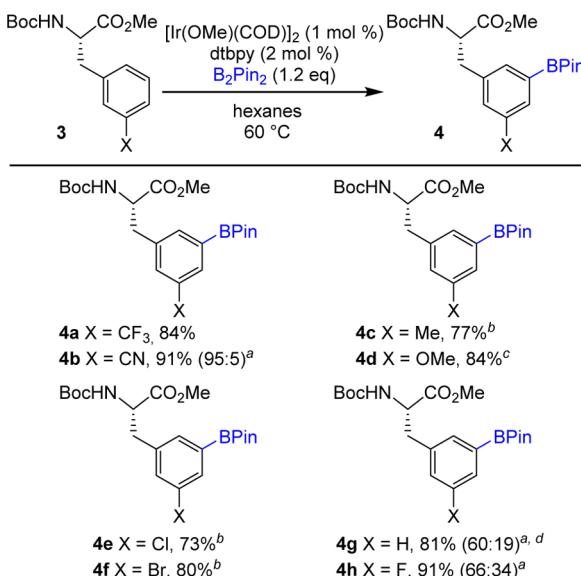
2.3.1.1. Borylation. Borylated organic compounds have become an important class of products. They are especially useful because they can be readily derivatized via the Nobel Prize winning Suzuki–Miyaura cross-coupling reaction. Efficient methodologies for the borylation of arenes and heteroarenes have therefore attracted considerable attention. An iridium-catalyzed C–H borylation alternative to the traditional palladium-catalyzed borylation of halides and pseudohalides was reported by Hartwig and Miyaura,³¹ as well as by Smith and Maleczka.³² Following their pioneering work on iridium-catalyzed C–H borylation of arenes and heteroarenes, Smith and Maleczka applied their findings to the regioselective C-2 borylation of *N*-Boc tryptophan methyl ester **1**, thus delivering the first example of C–H borylation of amino acids (Scheme 4).³³

Scheme 4. Iridium-Catalyzed C–H Borylation of Tryptophan³³



Using $[\text{Ir}(\text{OMe})(\text{COD})]_2$ as the catalyst, 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy), pinacolborane (HBPin), and bis(pinacolato)diboron (B_2Pin_2) in methyl *tert*-butyl ether (MTBE) at room temperature (rt) for 45 min, the desired product **2** was isolated in 43% yield together with starting material (31%). Although the C-2 borylated product was obtained in moderate yield, the authors indicated that the preparation of the monoborylated product was complicated by competing formation of diborylated product. Shortly after, Meyer et al.³⁴ reported the iridium-catalyzed C–H borylation of several amino acids. Various *meta*-substituted *N*-Boc phenylalanine methyl esters **3** were monoborylated in good to excellent yields (Scheme 5). The borylation almost exclusively occurred at the remaining *meta*-position of the ring to afford products **4**. Changing the *meta*-substituent from electron-withdrawing groups (products **4a** and **4b**) to electron-donating groups (EDG) (products **4c** and **4d**) did not affect the yield or the regiochemistry (ratio of 3,5- to 3,4-isomers 95:5). The presence of halides on the phenyl ring was well-tolerated as exemplified by the formation of products **4e** and **4f** in 73% and 80% yield, respectively. However, the use of protected phenylalanine (**4g**) or 3-fluorophenylalanine (**4h**), where the original *meta*-substituent is either absent or sterically undemanding, resulted in poorer regiocontrol with the ratios of 3,5- to 3,4-isomers decreasing to 60:19 and 66:34, respectively. This observation is in accordance with previous results denoting the importance of steric effects on the direct C–H borylation of simple arenes.

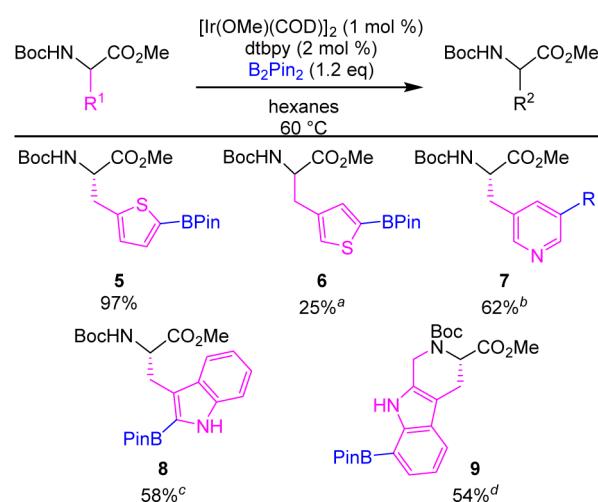
Scheme 5. Non-Directed Iridium-Catalyzed C–H Borylation of Substituted Phenylalanines^{34a}



^a(a) Yields correspond to isolated yields of a mixture of 3,5- and 3,4-isomers; ratios of 3,5-isomer determined by ¹H NMR are indicated in brackets; (b) using B_2Pin_2 (1.5 equiv) at 90 °C; (c) stereochemistry reversed from that shown as (*R*)-isomer was used; (d) yield also includes 21% of diborylated product.

Borylation of heteroarylalanine derivatives such as 2- and 3-thienylalanine, 3-pyridylalanine, and tryptophan was also described (Scheme 6). While 2-thienylalanine was readily borylated in the 5-position to give compound **5** in 97% yield, the highly reactive 3-thienylalanine underwent diborylation in the 2- and 5-position (α to the heteroatom). By using a reduced amount of B_2Pin_2 and decreasing the reaction temperature to 25 °C, the monoborylated product **6** could still be obtained

Scheme 6. Iridium-Catalyzed Borylation of Heteroaryl Amino Acids^{34a}

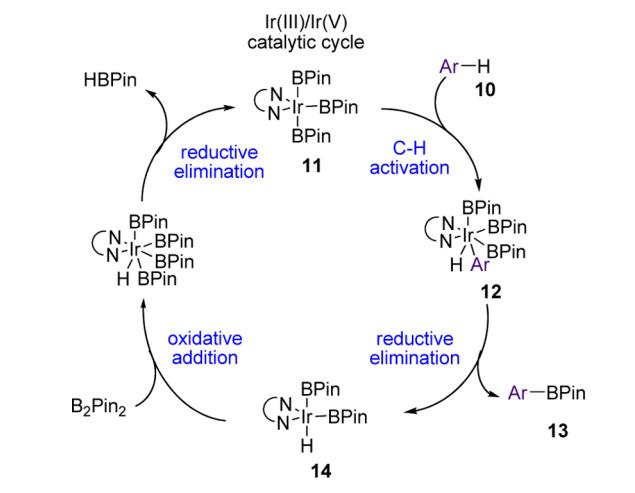


^a(a) Using B_2Pin_2 (0.5 equiv) at 25 °C; (b) yield corresponds to two steps (borylation followed by Suzuki reaction). R = *p*-nitrophenyl; (c) under MW in MTBE using $[\text{Ir}(\text{OMe})(\text{COD})]_2$ (1.5 mol %), dtbpy (3 mol %), and B_2Pin_2 (0.7 equiv); yield corresponds to a 6:1 mixture of **8** and 2,7-diborylated product (not shown); (d) using B_2Pin_2 (1.5 equiv) in tetrahydrofuran (THF) at 90 °C.

albeit in decreased yield (25% yield). Unlike the reactions with five-membered heterocycles, the C–H borylation of 3-pyridylalanine was sluggish; however, the use of elevated temperature yielded the preferred β -borylated product **7**. Similar to Smith and Maleczka,³³ Meyer et al.³⁴ found that the borylation of *N*-Boc tryptophan methyl ester predominantly afforded the 2-substituted product **8**. In the case where the 2-position was not available, the borylation of the 7-position was preferred as in compound **9**. In both studies, chiral high-performance liquid chromatography (HPLC) experiments were conducted to verify that the stereochemical integrity of the compounds was preserved after the borylation reaction. The boronate ester functional group introduced was found to be stable to peptide coupling conditions and could be directly reacted under Suzuki cross-coupling conditions. In addition, a “one-pot” procedure for the iridium-catalyzed C–H borylation/Suzuki reaction was also established.³⁴

The generally accepted iridium-catalyzed C–H borylation mechanism starts with the oxidative addition of the arene **10** to the (trisboryl)iridium(III) catalytic species **11**. The iridium(V) complex (**12**) thus formed undergoes reductive elimination of the desired borylated product **13**. The iridium(III) active species (**11**) is regenerated through oxidative addition of B_2Pin_2 to the iridium hydride (III) complex **14**, followed by reductive elimination of pinacolborane (Scheme 7).³⁵ The formation of such sterically congested hepta-coordinated Ir(V) intermediates accounts for the reaction sensitivity to steric factors.

Scheme 7. Iridium-Catalyzed C–H Borylation Mechanism

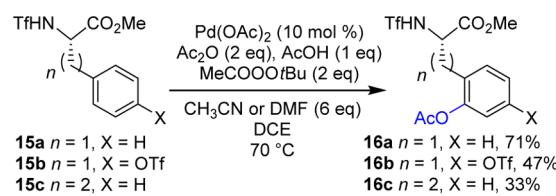


Recently, the Shie group has reported the palladium-catalyzed directed $C(sp^2)$ –H borylation of phenylalanine and arylglycine (see section 2.3.3.5).³⁶

2.3.1.2. Acetoxylation. Initially, due its potential application for the industrial production of methanol from the simplest alkane, the direct oxygenation of C–H bonds attracted considerable attention.³⁷ Despite the process not being economically viable, the regioselective C–H oxygenation of more complex molecules has been successfully achieved on a laboratory scale. Notably, the palladium-catalyzed *ortho*-acetoxylation of phenylalanine, tyrosine, and homophenylalanine directed by the *N*-triflame protecting group was reported by Vickers et al.³⁸ (Scheme 8).

$Pd(OAc)_2$ was employed as the catalyst at 10 mol % with *tert*-butyl peroxyacetate as the stoichiometric oxidant. Interestingly, the use of 6 equivalents of acetonitrile as an additive

Scheme 8. Palladium-Catalyzed Triflame Directed C–H Acetoxylation³⁸



resulted in a significant yield increase, but was found to be detrimental for highly reactive substrates as well as substrates lacking *ortho*-substitution. In those cases, *N,N*-dimethylformamide (DMF) could be used instead to afford a better ratio of mono- versus disubstituted product. Thus, by using DMF, phenylalanine **15a** and tyrosine **15b** were monoacetoxylated in 71% and 47% yield, respectively, while CH_3CN was required to effect the C–H acetoxylation of homophenylalanine **15c** in 33% yield.

The regioselective activation of the *ortho* C–H bond of phenylalanine (**15a**) and tyrosine (**15b**) presumably results from the formation of a six-membered palladacycle (**17a,b**). On the other hand, the remote C–H activation of homophenylalanine (**15c**) is believed to be dictated by a seven-membered metallacycle (**17c**), thus explaining the difference in reactivity between the two substrates. Although the authors do not advance a plausible reaction mechanism, during their studies on similar systems³⁹ they suggested a $Pd(II)/Pd(IV)$ type catalytic cycle (see Scheme 2) including the following steps: (a) insertion of $Pd(OAc)_2$ in the *ortho* C–H bond of the protected amino acid to form the six- or seven-membered ring palladacycle, **17a,b** or **17c**, respectively (Figure 1), (b)

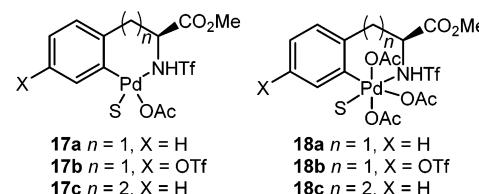


Figure 1. Palladium(II) and palladium(IV) metallacycle intermediates formed during the C–H acetoxylation reaction.

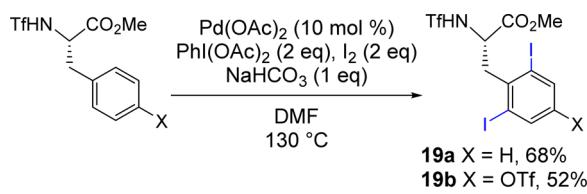
oxidation of the latter to the palladium(IV) intermediate (**18**), which readily undergoes (c) reductive elimination to afford the acetoxyated amino acid **16** and regenerate the active $Pd(II)$ species.

2.3.1.3. Halogenation. Interestingly, Li et al.⁴⁰ also reported that palladium-catalyzed C–H iodination could be achieved using $IOAc$ (generated *in situ* from $PhI(OAc)_2$ and I_2) as a stoichiometric oxidant. The same group applied this halogenation reaction to the synthesis of di-iodinated phenylalanine **19a** and di-iodinated tyrosine **19b** (Scheme 9).⁴¹

Again the triflame protecting group was employed as an efficient DG. The reaction mechanism is similar to that of the acetoxylation reaction ($Pd(II)/Pd(IV)$ catalytic cycle (see Scheme 2)), with the nuance that the initial $Pd(OAc)_2$ active species is not recycled after reductive elimination. PdI_2 , which has been found to be unreactive, is formed instead but is successfully converted back into the $Pd(OAc)_2$ catalyst by $IOAc$.

2.3.1.4. Arylation. Biaryls are arguably one of the most studied structural motifs. For example, this subunit is present in

Scheme 9. Palladium-Catalyzed Triflame Directed C–H Iodination⁴¹

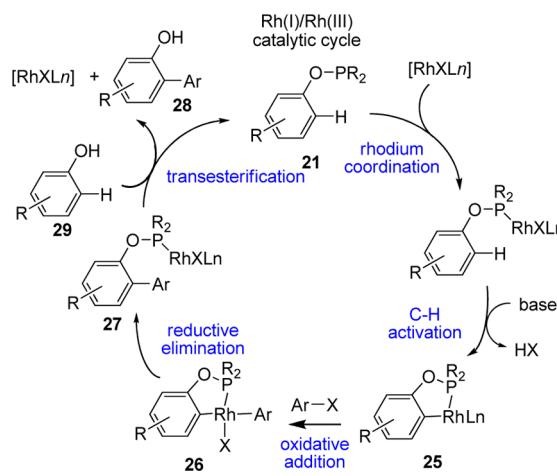


the glycopeptide antibiotic vancomycin, where the aryl–aryl bond between the side-chains of a tyrosine and a substituted phenylalanine forms one of the rings of this tricyclic molecule. The formation of similar *ortho*-arylated tyrosines through rhodium-catalyzed C–H activation has been reported by Bedford et al.⁴² and is illustrated in Scheme 10.

In an effort to functionalize the 2- and 6-positions of the aromatic ring with different aryl groups, Bedford et al.⁴² first masked the C–H bond in position 2 of Boc-L-Tyr-OMe with a bulky *tert*-butyl group. Subsequent selective monoarylation of compound 20 was successfully achieved with various aryl bromides, using 5 mol % of Wilkinson's catalyst ($[\text{RhCl}(\text{PPh}_3)_3]$), 15 mol % of cocatalytic phosphinite 21 [$\text{PR}_2(\text{OAr})$] prepared from PR_2X and the phenol starting material], and Cs_2CO_3 in toluene, in acceptable to excellent yields. After removal of the *tert*-butyl group with $\text{AlCl}_3\text{--MeNO}_2$ and reinstalment of the methyl ester and Boc protecting groups, attempts to effect the second C–H arylation of compound 22b either proceeded in low yield or provided a mixture of product 23 and undesired side-product 24 resulting from further alkylation. Furthermore, the authors indicated that complete epimerization occurred during the installation of the *tert*-butyl group, thus rendering the determination of the effect of the C–H arylation reaction on the stereochemistry impossible.

The selective arylation of phenols was previously published by the same group⁴³ and is believed to proceed through the following mechanism (Scheme 11): (a) coordination of the metal to the phosphine atom of $\text{PR}_2(\text{OAr})$ 21 followed by *ortho*-metallation to yield 25, (b) oxidative addition of the aryl halide to the metal to form a rhodium(III) complex (26), (c) reductive elimination releasing the arylated phosphinite 27, and (d) formation of the desired *ortho*-arylated phenol 28 by transesterification of the newly formed phosphinite 27 with the

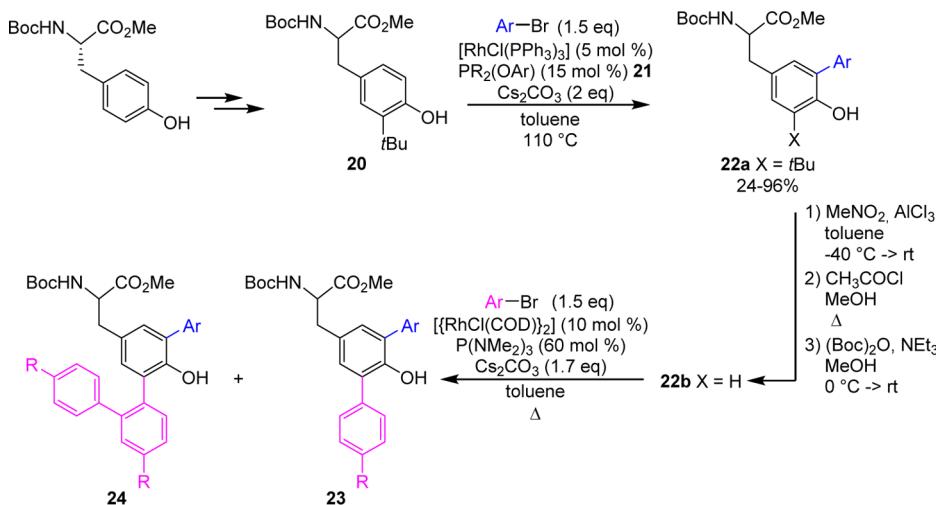
Scheme 11. Rhodium-Catalyzed C–H *ortho*-Arylation of Phenols

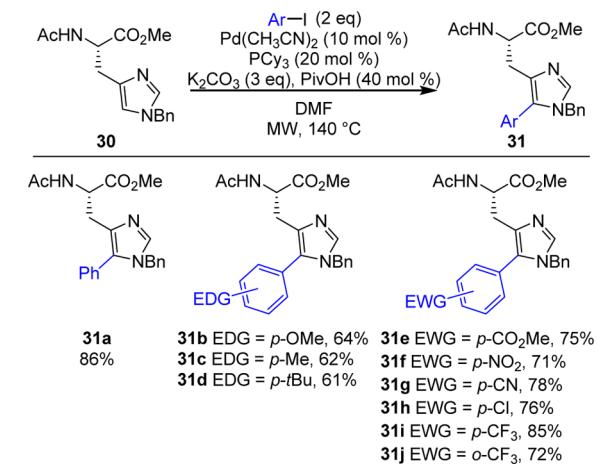


starting material 29 and regeneration of the active catalyst. An alternative mechanism where the oxidative addition step precedes the C–H activation step is also plausible.

Examples of C–H arylation of tryptophan and histidine have also appeared recently. Mahindra et al.⁴⁴ published the C–H arylation of Ac-His(Bn)-OMe 30 under microwave (MW) irradiation (Scheme 12). The more nucleophilic C-5 position was selectively arylated and afforded products 31 in good yields when aryl iodides were employed as coupling partners. The use of aryl bromides also afforded the desired products, albeit only poor yields were obtained (<18% yield). The following optimized conditions, 10 mol % $\text{Pd}(\text{CH}_3\text{CN})_2$, 20 mol % PCy_3 , K_2CO_3 , and 40 mol % PivOH in DMF, were identified after screening of various reaction parameters and were found to promote the C-5 arylation of 30 with phenyl iodide in 86% yield (31a). Interestingly, using $\text{Pd}(0)$ instead of $\text{Pd}(\text{II})$ catalysts was found to be detrimental to effect conversion to product; the same trend was observed when PCy_3 was replaced with bulkier phosphine ligands. Finally, when stronger bases were employed, only a trace amount of the desired arylated product was observed. Aryl iodides bearing both electron-donating and electron-withdrawing substituents were well-tolerated as exemplified by the preparation of compounds

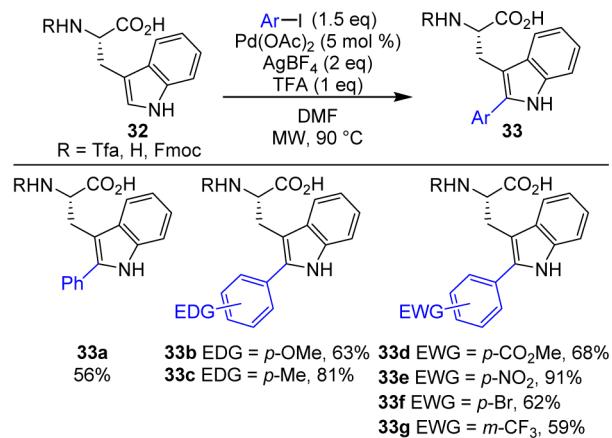
Scheme 10. Rhodium-Catalyzed *ortho*-Arylation and Diarylation of Tyrosine⁴²



Scheme 12. Palladium-Catalyzed Arylation of Histidine⁴⁴

31b–d (61–64% yields) and compounds **31e–j** (71–85% yields), respectively. Chiral HPLC analysis confirmed that no racemization occurred during the arylation reaction.

Similarly, Preciado et al.⁴⁵ reported the selective C-2 arylation of *N*^α-trifluoroacetyl (Tfa), *N*^α-fluorenylmethoxy-carbonyl (Fmoc), or free tryptophan **32** with a wide range of aryl iodides using 5 mol % Pd(OAc)₂, 2 equivalents of AgBF₄, and trifluoroacetic acid (TFA) in DMF under MW irradiation (Scheme 13).

Scheme 13. Palladium-Catalyzed Arylation of Tryptophan⁴⁵

The synthesis of arylated tryptophan **33** was achieved in moderate to excellent yields (56–91% yields) when using aryl iodides, with the exception of 2-thienyl iodide, which only afforded a poor conversion (<15%). These relatively mild reaction conditions were found to preserve the stereochemistry of the amino acid starting material.

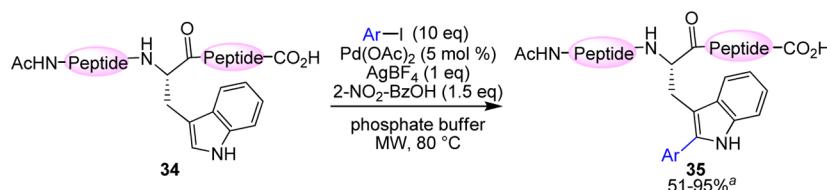
Interestingly, on the basis of previous work by the Fagnou group,³⁰ Mahindra et al.⁴⁴ proposed a Pd(0)/Pd(II) catalytic cycle for the arylation of histidine (see Scheme 2), in which the aryl iodide first undergoes oxidative addition to a Pd(0) species generated in situ from the Pd(II) precatalyst and PCy₃. The following step consists of the insertion of the Pd(II) complex into the C–H bond. Finally, reductive elimination of the desired arylated product liberates the Pd(0) active catalyst and closes the catalytic cycle. Preciado et al.⁴⁵ suggested, however, that under the reaction conditions they described, the arylation of tryptophan would most likely follow a Pd(II)/Pd(IV) cycle (see Scheme 2), but did not rule out a plausible Pd(0)/Pd(II) manifold. Both authors postulate that the C–H bond cleavage occurs through a concerted metallation deprotonation step,²⁹ thus explaining the critical role of the TFA and PivOH additives, respectively. Additionally, Preciado et al.⁴⁵ suggested that coordination of the free carboxylic acid of tryptophan could be assisting the metallation step through the formation of a palladacycle.

The silver salt in the protocol reported by Preciado et al.⁴⁵ also appears to be primordial for the catalytic cycle. Silver salts are commonly used in similar reactions as halide scavengers, and have been suggested to abstract the iodide from the Pd(IV) complex, thus allowing the carboxylate anion to coordinate with the metal, rendering it more electrophilic and therefore facilitating the reductive elimination step. An alternative mechanism would involve the reductive elimination to occur releasing an inactive PdI₂ species prior to regeneration of the active catalyst and silver iodide formation (see Scheme 2). The TFA is also believed to protonate the amino group of the unprotected nitrogens, thus preventing undesirable coordination and allowing the reaction to proceed even when the α -amino group remains free.

The process described by Preciado et al.⁴⁵ is of particular interest because it allows for the one-step derivatization of Fmoc-Trp-OH, affording non-proteinogenic amino acids appropriately protected for direct incorporation into the peptide chain by Fmoc solid-phase peptide synthesis (SPPS).

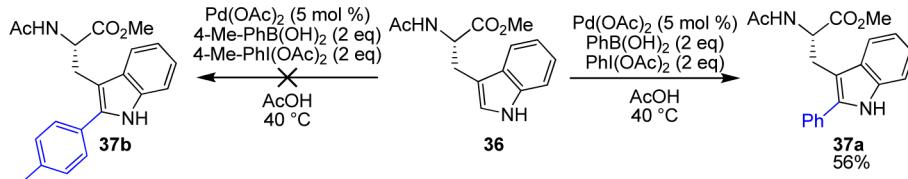
Alternatively, the same group also reported the selective arylation of tryptophan-containing peptides.⁴⁶ Tri- and tetrapeptides (**34**) designed to encompass all types of functional groups commonly found in proteinogenic amino acid side-chains and presenting an acetylated *N*-terminus were reacted with a 10-fold excess of aryl iodides in phosphate buffer (pH 6) at 80 °C under MW irradiation (Scheme 14).

While peptides containing aromatic, acidic, and basic side-chains were successfully monoarylated to yield compounds **35**, peptides containing sulfur amino acids suffered from peptidic cleavage. Interestingly, the selective monoarylation of tryptophan was found to be independent of the position of the tryptophan residue within the peptide sequence and took place

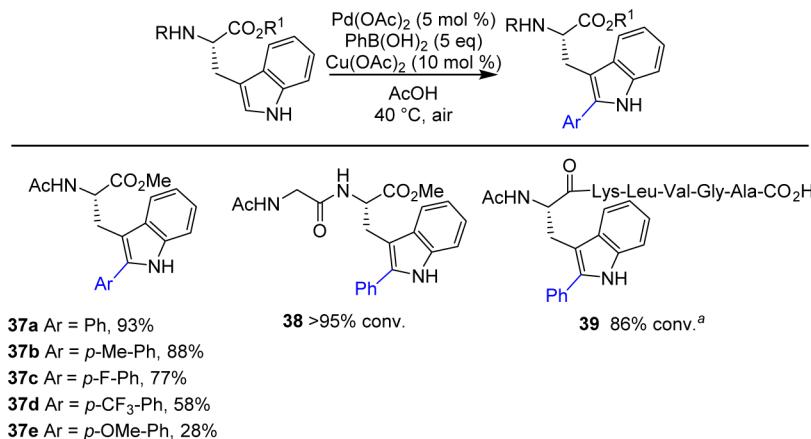
Scheme 14. Palladium-Catalyzed Arylation of Tryptophan-Containing Peptides^{46a}

^a(a) Yields were calculated by integration of HPLC peaks.

Scheme 15. Palladium-Catalyzed Arylation of Tryptophan Using Sanford's Conditions⁴⁷



Scheme 16. Palladium-Catalyzed C–H Arylation of Tryptophan and Tryptophan-Containing Peptides Using Mild Conditions^{47a}



^a(a) Using Pd(OAc)₂ (30 mol %) and Cu(OAc)₂ (60 mol %).

even when histidine was present in the amino acid sequence of the peptide.

Another example of non-directed tryptophan C(sp²)–H arylation was recently reported by the Fairlamb group.⁴⁷ They first employed Sanford's arylation conditions⁴⁸ and reacted N-acetyl methyl ester tryptophan 36 with a diaryl iodonium salt, formed *in situ* by PhB(OH)₂ and PhI(OAc)₂. The desired arylated product 37a was obtained in 56% yield. However, switching from PhB(OH)₂ to 4-Me-PhB(OH)₂ failed to provide the arylated product 37b, and only the homocoupled product could be isolated (Scheme 15).

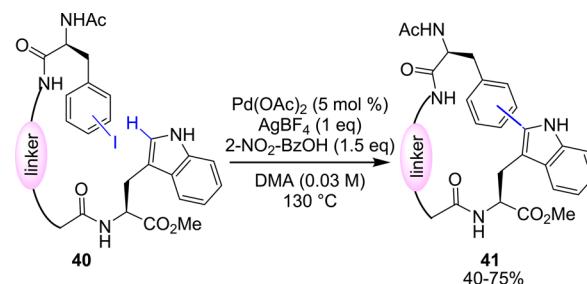
Replacing PhI(OAc)_2 by Cu(OAc)_2 and O_2 as a co-oxidant afforded a milder and more general procedure. Applying these new conditions, compound **37b** was formed in 88% yield, and the yield of product **37a** was improved to 93% yield. In addition, boronic acids substituted by a fluorine atom and the CF_3 EWG also successfully reacted affording products **37c** and **37d** in 77% and 58% yield, respectively. However, using electron-rich 4-MeO- PhB(OH)_2 , product **37e** was only obtained in modest yield (28% yield). Furthermore, the Fairlamb group also described the site-specific arylation of tryptophan-containing peptides.⁴⁷ Using the same arylation conditions, the *N*-Ac-Gly-Trp-CO₂Me dipeptide was arylated to give **38** in 95% conversion. The arylation of a longer peptide, *N*-Ac-Trp-Lys-Leu-Val-Gly-Ala-CO₂H, under these conditions also afforded the desired compound **39** in 86% conversion, albeit higher palladium-catalyst and copper-oxidant loadings were necessary (30 mol % and 60 mol %, respectively). The palladium-catalyzed C–H arylation of tryptophan and a tryptophan-containing peptide residue using the mild conditions developed by Fairlamb and co-workers are depicted in Scheme 16.

Interestingly, Fairlamb and co-workers observed and characterized the Pd(0)-nanoparticles formed *in situ* in the

early stage of the reaction.⁴⁷ Furthermore, the Fairlamb group was able to catalyze the arylation reaction using presynthesized encapsulated palladium particles; thus they postulated that Pd(OAc)₂ could act as a precatalyst for the formation of the Pd(0)-nanoparticle active species.

Finally, the C-2 arylation of tryptophan has recently been employed as a new technique for side-chain to side-chain peptide macrocyclization.⁴⁹ Tryptophan-containing "peptides" (**40**) (tryptophan connected to another amino acid via a linker) were intramolecularly arylated with *para*- or *meta*-iodophenylalanine to form 15- to 25-membered rings (**41**) as depicted in Scheme 17.

Scheme 17. Macrocyclization via Intramolecular Palladium-Catalyzed C–H Arylation of Tryptophan⁴⁹



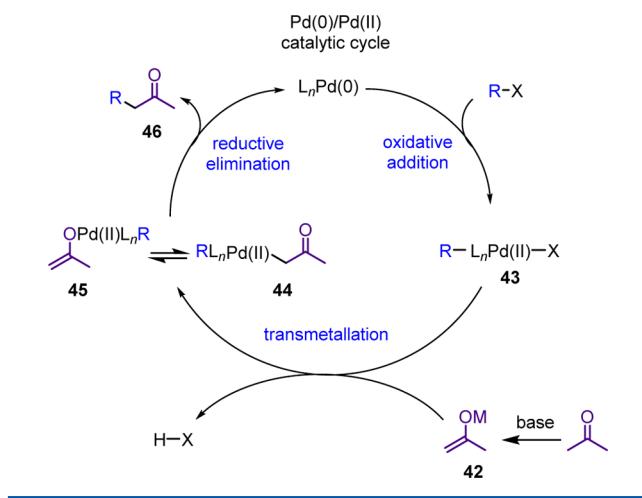
While peptide containing *meta*-iodotyrosine successfully cyclized (58% yield), the use of *ortho*-substituted iodophenylalanines failed to afford the macrocyclic product. The peptides protected at both the *N*- and the *C*-terminus were cyclized in solution using 5 mol % Pd(OAc)₂, AgBF₄, and 2-nitrobenzoic acid in *N,N*-dimethylacetamide (DMA) (0.03 M) at 130 °C under MW heating. Interestingly, high-dilution conditions were not necessary to achieve good yields of the desired cyclic

peptides. Although this novel technique appears to be practical, it remains to be tested on complex peptide substrates.

2.3.2. Functionalization of Activated C(sp³)–H Bonds.

2.3.2.1. Arylation. In addition to the reactivity of C(sp²)–H bonds, the intriguing reactivity of activated C(sp³)–H bonds has also been exploited for the synthesis of amino acids. C(sp³)–H bonds α to carbonyl functional groups are among the most widely used activated C(sp³)–H bonds for transition metal-catalyzed C–H functionalization reactions.^{22c} Indeed, as described in Scheme 18, in the presence of a base such

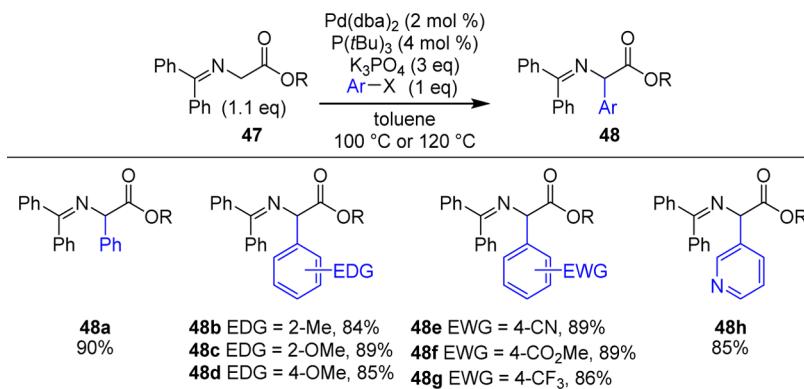
Scheme 18. Catalytic Cycle of Palladium-Catalyzed α -Arylation of C(sp³)–H Bond α to Carbonyl



compound will form enolate intermediate 42, capable of undergoing transmetalation with palladium complex 43, previously obtained through oxidative addition of Pd(0) active species with aryl halide. Intermediate 44 thus formed exists in equilibrium with its tautomer 45. Finally, reductive elimination affords the α -arylated carbonyl product 46.^{22c}

Hartwig and co-workers first applied the palladium-catalyzed α -arylation of enolate to imine-protected glycinate templates, thus providing a versatile synthesis of α -arylated amino acids by direct introduction of the side-chain.⁵⁰ Using O'Donnell's N-(diphenylmethylene)glycinate 47 in conjunction with Pd(dba)₂ as a catalyst, the sterically hindered P(tBu)₃ ligand, and K₃PO₄ as a mild base in toluene at 100 or 120 °C, they successfully obtained the products of the monoarylation with a wide range of aryl bromides and aryl chlorides (Scheme 19).

Scheme 19. Pd-Catalyzed α -Arylation of N-(Diphenylmethylene)glycinate⁵⁰



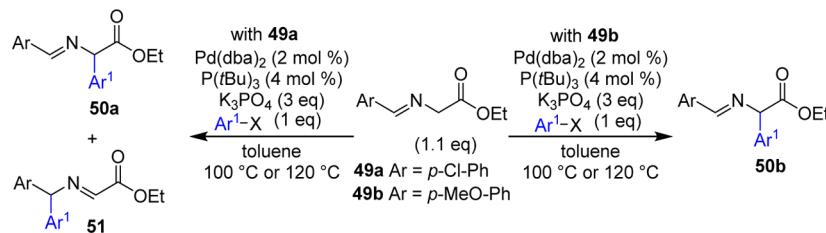
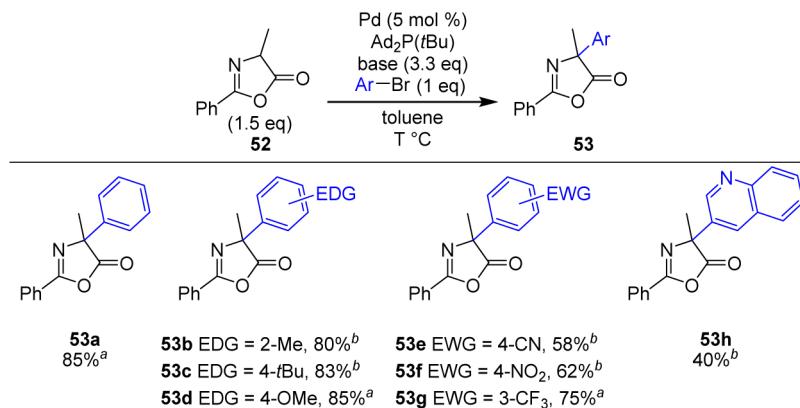
While phenylglycine derivative 48a was obtained in 90% yield, arylglycine derivatives bearing electron-donating groups 48b–d were also formed in good yields (84–89% yields). Furthermore, the reaction does not seem to be influenced by steric hindrance as highlighted by the formation of compounds 48b and 48c (84% and 89% yield, respectively) both bearing substituents at the *ortho* position. Changing to electron-withdrawing substituents did not impact the reactivity. Compounds 48e, 48f, and 48g presenting *p*-CN, *p*-CO₂Me, and *p*-CF₃ substitutions could be obtained in 89%, 89%, and 86% yield, respectively. Notably, heteroaryl halides were also found to be suitable coupling partners, as demonstrated by the preparation of 3-pyridylglycine 48h in 85% yield.

Interestingly, when substituting 47 with ethyl *N*-(*p*-chlorobenzylidene)glycinate (49a), a second product was observed, which was identified as the product from the arylation at the imine carbon (51). Switching 49a for *N*-(*p*-methoxybenzylidene)glycinate 49b efficiently disfavored this side-reaction, and only the desired monoarylated product 50b was formed (Scheme 20). However, using these less hindered aldimine-protected glycinate starting materials, attempt to prepare quaternary amino acids remained unsuccessful.

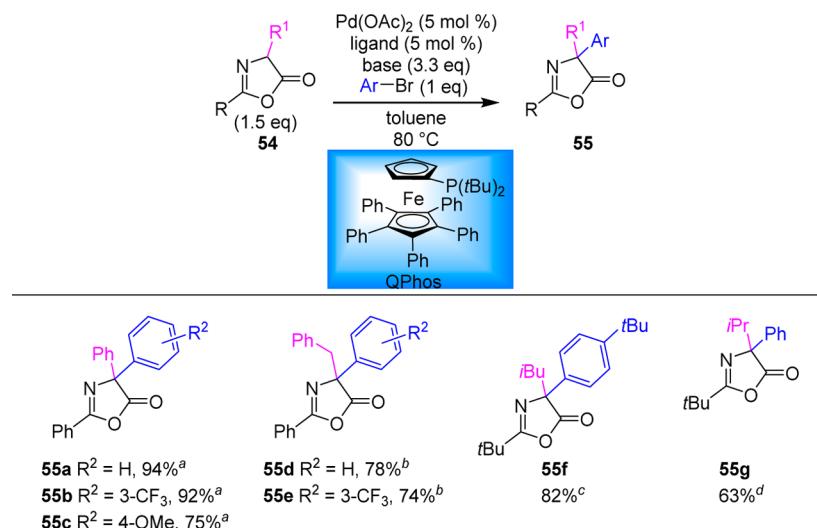
Later, the same group reported the palladium-catalyzed α -arylation of azlactones to form quaternary amino acids.⁵¹ While reactions with imine-protected α -substituted amino acids failed to deliver quaternary amino acids, azlactones, which present more acidic α -protons and are less hindered due to their cyclic structures, were found to be suitable substrates. The results of the palladium-catalyzed arylation of the azlactone derived from alanine (52) with aryl bromides are represented in Scheme 21.

The reaction with phenyl bromide afforded product 53a in 85% yield; similar yields were observed for the reaction of phenyl bromides bearing electron-neutral to electron-donating substituents. Thus, compounds 53b–d were prepared in yields ranging from 80% to 85%. However, slightly lower yields were obtained with phenyl bromides decorated with electron-withdrawing groups (53f,g, 58–75% yields). Although the coupling with various bromopyridyl reagents failed, compound 53h resulting from the coupling of 3-bromoquinoline was formed in a moderate 40% yield.

Furthermore, the reactions of azlactones derived from other amino acids (54) were also investigated. Although good yields could be obtained with arylglycine, phenylalanine, leucine, and valine, the choice of the optimal catalytic system was found to be substrate dependent (Scheme 22).

Scheme 20. Pd-Catalyzed Arylation of *N*-(*p*-Chlorobenzylidene)glycinate and *N*-(*p*-Methoxybenzylidene)glycinate⁵⁰**Scheme 21.** Palladium-Catalyzed α -Arylation of Azlactone Derived from Alanine^{51a}

^a(a) Using **52** (1.5 equiv), Pd(OAc)₂, Ad₂PtBu (5 mol %), and K₃PO₄ at 80 °C; (b) using **52** (2 equiv), Pd(dba)₂, Ad₂PtBu (10 mol %), and K₂CO₃ at 100 °C.

Scheme 22. Palladium-Catalyzed α -Arylation of Azlactones Derived from Various Amino Acids^{51a}

^a(a) Using **54** (1.5 equiv), QPhos, and K₂CO₃ at 80 °C; (b) using **54** (1.5 equiv), Ad₂PtBu, and K₃PO₄; (c) using Ad₂PtBu (10 mol %); (d) using Ad₂PtBu (10 mol %) at 100 °C.

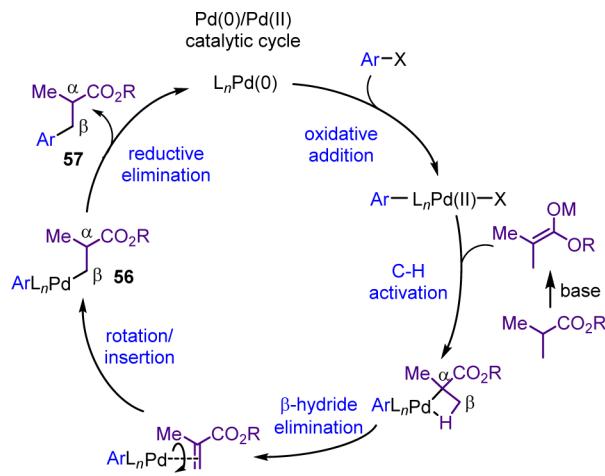
The coupling of the azlactone derived from arylglycine with phenyl bromide and phenyl bromides substituted with electron-withdrawing as well as electron-donating groups proceeded with 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene (QPhos) as the ligand and K₂CO₃ as the base, yielding product **55a–c** in 75–94% yields. On the other hand, the optimal conditions for the coupling of the azlactone derived from phenylalanine with phenyl bromide and 3-CF₃-phenyl bromide were obtained by using Ad₂PtBu and K₃PO₄ instead. With the second set of conditions, products **55d** and **55e** were formed in 78% and 74% yield, respectively. In the case of the azlactones

derived from leucine and valine, it was found that replacing the 2-phenyl substituent of the azlactone by a *tert*-butyl group greatly improved the yields. Thanks to this modification, the synthesis of compounds **55f** and **55g** was achieved in 82% and 63% yield, respectively.

In addition to the traditional α -arylation, the β C(sp³)–H arylation of ester enolates was introduced by the group of Prof. Baudoin.⁵² Unlike the classical α -arylation mechanism, two consecutive steps, the β -hydride elimination and rotation insertion, are believed to promote the migration of the palladium from the α to the β C(sp³)–H bond where the

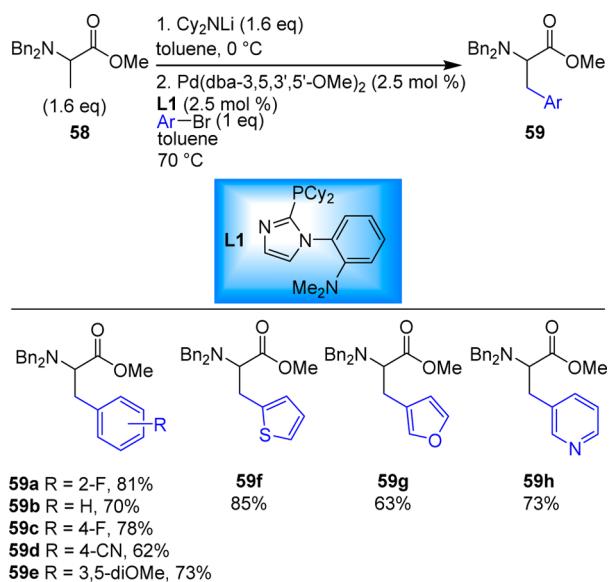
palladium complex **56** undergoes faster reductive elimination, thus affording the β -arylated product **57**.⁵² The proposed catalytic cycle is highlighted in Scheme 23.

Scheme 23. Catalytic Cycle of Palladium-Catalyzed β -Arylation of C(sp³)–H Bond β to Carboxylic Ester⁵²



This methodology was applied to *N*-dibenzyl protected alanine methyl ester **58**.⁵³ Unlike the β C(sp³)–H arylation of ester enolates, this reaction was not limited to aryl bromides bearing an electron negative substituent at the *ortho* position. Using Pd(dba-3,5,3',5'-OMe)₂ as the catalyst and the novel phosphine ligand **L1** in conjunction with lithium dicyclohexylamide as the base, **58** was successfully reacted with various (hetero)aryl bromides as represented in Scheme 24. As

Scheme 24. β C(sp³)–H Arylation of N-Dibenzyl Protected Alanine Methyl Ester⁵³

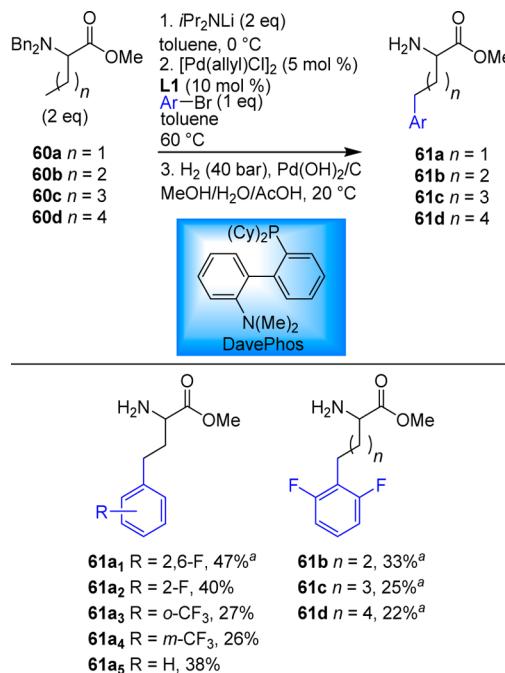


expected, compound **59a**, produced by the β -arylation with 2-fluorophenyl bromide, was obtained in high yield. The phenylalanine derivative **59b** was also formed in a high 70% yield. Furthermore, 4-fluorophenyl bromide, which only afforded a complex mixture of α and β -arylation when reacted with carboxylic esters, provided the clean product of β -arylation **59c** in 78% yield when reacted with **58**. Other substitutions at

the *meta*- and *para*-positions with electron-withdrawing (**59d**, 62% yield) and electron-donating groups (**59e**, 73% yield) were also well-tolerated. Valuable heteroarylalanine derivatives were readily prepared in good yields. In detail, the synthesis of 2-thienylalanine **59f** and 3-furanalanine **59g** was achieved in 85% and 63% yield, respectively. Interestingly, while using 3-pyridyl bromide failed to deliver any β -arylation when reacted with carboxylic ester,⁵² 3-pyridylalanine could be prepared in synthetically useful yield (**59h**, 73% yield) by reacting the same bromide with **58**. This further illustrates the different reactivity of the protected alanine and the carboxylic ester templates.

In addition to the β -arylation of alanine derivatives, Baudoin and co-workers extended the reaction to long-range arylation of amino acids bearing longer alkyl chains (**60a–d**).⁵³ The arylation was shown to take place at the terminal 1° C(sp³)–H bond, albeit solely aryl bromides bearing electronegative *ortho*-substituents could be successfully employed. Furthermore, lower yields and regioselectivities were obtained. The desired products could be separated from the unwanted arylated side-products by chromatography after the removal of the benzyl protecting groups by hydrogenolysis (Scheme 25). Reaction with the most favorable 2,6-difluorophenyl

Scheme 25. Long-Range γ to ϵ C(sp³)–H Arylation of Alkyl Amino Acids Derivatives^{53a}



^a(a) Using 2-dicyclohexylphosphino-2'-(*N,N'*-dimethylamino)-biphenyl (DavePhos) and Cy_2NLi .

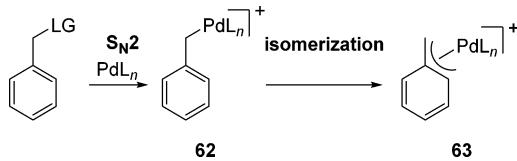
bromide gave moderate yield of the desired debenzylated product **61a**₁ (47% yield). Using the phenyl bromide bearing single fluorine at the *ortho* position led to a slight decrease in the yield (**61a**₂, 40% yield). The presence of the least electron-deficient CF₃ group at the *ortho* position resulted in the desired product **61a**₃ being formed in only 27% yield. Phenyl bromides lacking electron-deficient substituent in that position still afforded the product of the γ -arylation as exemplified by **61a**₄ and **61a**₅, albeit in low yields. Increasing the size of the alkyl chain resulted in the expected δ , ϵ , ζ -arylation, with

progressively lower yields as the length of the chain increased (**61b–d**, 33–22% yields). Nevertheless, other phenyl bromides than 2,6-difluorophenyl bromide only afforded complex mixtures of arylated products.

Despite these methodologies being of interest, an enantioselective version of the reactions remains to be established.

2.3.2.2. Benzylation. Building on their seminal work on enantioselective transition metal-catalyzed allylation of azlactones,⁵⁴ Trost and co-workers recently described the asymmetric palladium-catalyzed benzylation of azlactones using chiral bidentate phosphine ligands.⁵⁵ Benzylic diethylphosphates were employed as the electrophile. Their ionization by the metal leads to the cationic dearomatized η^3 -benzyl palladium intermediate, which then follows the usual trans-metallation, reductive elimination steps of the catalytic cycle. A plausible mechanism for the formation of the intermediate **63** would encompass the displacement of the leaving group (LG) by the palladium via a nucleophilic substitution of order 2 (S_N2), followed by the isomerization of the σ -bond palladium complex **62** (Scheme 26).⁵⁵

Scheme 26. Plausible Mechanism for the Formation of the η^3 -Benzyl Palladium Intermediate⁵⁵

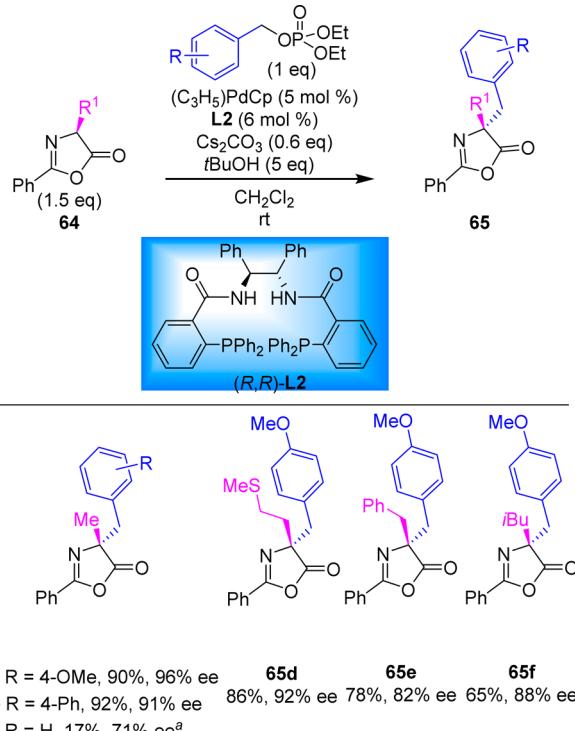


Trost and co-workers' initial results using azlactones derived from various amino acids in conjunction with electron-rich benzyl phosphates are described in Scheme 27.

Azlactone derived from alanine was reacted with various substituted benzyl phosphates. As expected, benzyl phosphates presenting electron-donating *p*-methoxy and *p*-phenyl functionalities on the aryl ring reacted more readily to yield the desired products **65a** and **65b** in 90% and 96% yield, respectively, and high enantiomeric excess (ee) (96% and 91% ee, respectively). However, the product of the reaction with unsubstituted benzyl phosphate **65c** was only formed in low yield (17% yield) and moderate enantioselectivity (71% ee). High yield and ee were also achieved in the benzylation of the azlactone derived from methionine with *p*-methoxybenzyl diethyl phosphate (**65d**, 86% yield, 92% ee). Finally, both yields and ee slightly decreased when the azlactone derived from phenylalanine and leucine were employed (**65e**, 78% yield, 82% ee; and **65f**, 65% yield, 88% ee).

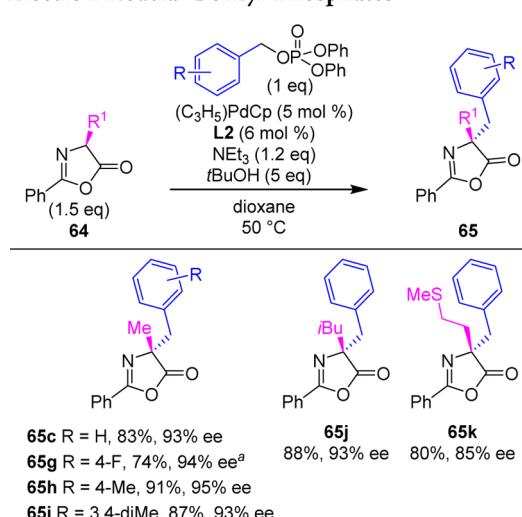
Following a screening of various reaction parameters, optimal reaction conditions were determined, which extended the scope of electrophiles to electron-neutral diphenyl benzyl phosphates (Scheme 28). Employing a more labile diphenyl phosphate as the leaving group, triethylamine as the base, and dioxane as the solvent at 50 °C greatly enhanced the scope of suitable benzylphosphate electrophiles. Product **65c**, which was only obtained in 17% yield under the previous reaction conditions, could be isolated in 83% yield in an improved 93% ee. Furthermore, compounds **65g** and **65h** decorated with *para*-fluoro and *para*-methyl functionalities were prepared in 74% and 91% yield, respectively, and in excellent ee. Dimethyl substitution was also tolerated as demonstrated by the formation of **65i** in 87% yield and 93% ee. Finally, the benzylation of azlactone derived from leucine and methionine

Scheme 27. Palladium-Catalyzed Benzylation of Azlactones with Electron-Rich Benzyl Phosphates^{55a}



^a(a) Stereochemistry reversed from that shown as (S,S) -**L2** was employed.

Scheme 28. Palladium-Catalyzed Benzylation of Azlactones with Electron-Neutral Benzyl Phosphates^{55a}



^a(a) Reaction conducted at 25 °C.

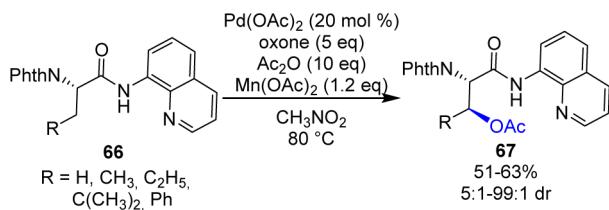
with benzyl diphenylphosphate was also investigated, and once again products **65j** and **65k** were obtained in high yields (88% and 80% yield, respectively) and high ee.

2.3.3. Functionalization of Unactivated C(sp³)–H Bonds. In addition to the impressive advances in C–H functionalization of C(sp²)–H bonds and C–H functionalization of activated C(sp³)–H, the more challenging C–H functionalization of unactivated C(sp³)–H bonds has also witnessed significant progress. Thanks to the development of

efficient DGs, the C–H functionalization of chiral aliphatic amino acids in β - and γ -positions has now been successfully achieved. The acetoxylation, arylation, alkenylation, and alkylation of unactivated 1° C(sp³)–H and to an extent unactivated 2° C(sp³)–H bonds have recently appeared in the literature. These represent a practical strategy for the structural diversification of aliphatic amino acids.

2.3.3.1. Acetoxylation. E. J. Corey's research group first described the C–H acetoxylation of the C(sp³)–H bond of protected amino acids.⁵⁶ A phthaloyl (Phth) group was used to protect the α -amino functionality while various carboxamide DGs were investigated. Among the N-methoxyamide, Weinreb amide, oxazoline, picolinamide, pyridin-2-ylmethanamine, and 8-aminoquinoline DGs tested, only the 8-aminoquinoline group, originally developed by the Daugulis group,⁵⁷ provided promising results. Leucine, alanine, homoalanine, norvaline, and phenylalanine appropriately protected (**66**) were successfully β -acetoxylated to afford products **67** in good yields (51–63% yields) with good diastereoselectivity (from 5:1 to 99:1 S,S:S,R) using the following conditions: Pd(OAc)₂, oxone, Ac₂O, and Mn(OAc)₂ in CH₃NO₂ (Scheme 29).

Scheme 29. Palladium-Catalyzed 8-Aminoquinoline-Directed C–H Acetoxylation of C(sp³)–H Bonds in Amino Acids⁵⁶



Although the reaction still proceeds when tBuOOH was used as an oxidant, only recovered starting material was isolated in the absence of Mn(OAc)₂. Furthermore, the use of PhI(OAc)₂ also failed. The authors postulated that Mn(OAc)₂ could be oxidized to Mn₃O(OAc)₇, which would act as a Lewis acid increasing the Pd electrophilicity, thus facilitating its insertion into the C–H bond. Interestingly, in substrates such as homoalanine, the C–H acetoxylation is regiospecific, and no product resulting from γ -acetoxylation of the 1° C(sp³)–H bond was observed. Daugulis et al.⁵⁷ postulated the formation of a metallacycle intermediate in which the 8-aminoquinoline acts as a bidentate DG chelating the metal and facilitating the extremely difficult activation of the β - 2° C(sp³)–H bond by the formation of a double five-membered palladacycle. In addition, Corey et al.⁵⁶ suggested that the stereoselectivity of the β -functionalization could be the result of the sterically preferred formation of a *trans*-palladacycle where the N-Phth and the R group adopt a *trans*-orientation as shown in Figure 2.

2.3.3.2. Arylation. Encouraged by the results obtained from the acetoxylation reaction, the Corey group subsequently investigated the C(sp³)–H β -arylation of *N*-phthaloyl amino

acids (**68**)⁵⁶ using reaction conditions adapted from previous findings by Daugulis et al.⁵⁸ (Scheme 30). While amino acids presenting a 2° C(sp³)–H bond in the β -position such as leucine and phenylalanine were successfully monoarylated in high yields with several aryl iodides (**69a–d** and **69e,f**, respectively), alanine that exhibits a 1° C(sp³)–H bond was fully diarylated to give **69g**. Furthermore, the arylation of isoleucine and valine, which bear a 3° C(sp³)–H bond with *p*-iodoanisole, gave rise to the mono- γ -arylated products **69h** and **69i** in high yields. Interestingly, under the same reaction conditions, the β - 4° amino acid α -*tert*-butylglycine led to a mixture of mono- and diarylated products (**69j**).

Building on this original report, Tran and Daugulis demonstrated the use of 2-thiomethylaniline as a DG for the β -monoarylation of alanine with aryl and heteroaryl iodides.⁵⁹ Thus, by changing the DG from 8-aminoquinoline to 2-thiomethylaniline, they could prepare the mono- or diarylated alanine derivatives, respectively, as depicted in Scheme 31.

Despite facilitating highly regioselective C–H functionalization, the use of DGs thus far suffered from the lack of practical reaction conditions to effect their removal. Tran and Daugulis also described mild conditions for the removal of the 8-aminoquinoline as well as the 2-thiomethylaniline DGs, affording the *N*-phthaloyl methyl ester compounds **70** in excellent ee (Scheme 32).⁵⁹

Inspired by the work of Daugulis, several research groups have focused their attention on the development of what has become a collection of new bidentate DGs. Among them, the Shi group has reported the use of 2-(pyridin-2-yl)-isopropylamine⁶⁰ as an alternative to the 8-aminoquinoline and 2-thiomethylaniline previously described. As part of their study on the development of a C–H functionalization strategy for the synthesis of *N*-heterocycles, Shi and co-workers employed the 2-(pyridin-2-yl)isopropyl (PIP) DG to achieve the selective monoarylation of the β - 1° C(sp³)–H bond of alanine **71**, followed by the intramolecular amidation of the resulting 2° C(sp³)–H bond **72**. Their sequential approach to α -amino- β -lactams **73** is depicted in Scheme 33.

Unlike the 2-thiomethylaniline and the 8-aminoquinoline, the PIP DG was able to afford the monoarylated product in high selectivity during the first reaction step while being stable to the oxidation conditions employed during the amidation step. A wide range of aryl iodides and even heteroaryl iodides were successfully reacted, yielding phenylalanine derivatives in high yields and excellent selectivity. However, the use of aryl bromides failed to deliver the desired products. Finally, the PIP DG could be cleaved through a mild *N*-nitrosylation/hydrolysis sequence without loss of ee.

The selective γ -arylation of C(sp³)–H bonds has also been achieved thanks to the use of DGs. Such remote functionalization requires the installation of the DG onto the amine functionality. The picolinamide derived from the picolinoyl (PA) DG originally reported by Daugulis and co-workers⁵⁷ was successfully employed by He and Chen for the γ -monoarylation of cyclohexylamino acid **74a** with various (hetero)aryl iodides in moderate to good yields (Scheme 34).⁶¹ Unfortunately, no reaction occurred when 4-iodopyridine was used. Because of the difficulty they encountered during the cleavage of the DG, He and Chen developed a modified-picolinoyl DG (**74b**) bearing a methylene hydroxyl function, capable of facilitating the amide bond cleavage through intramolecular acyl transfer.

More recently, the Carretero⁶² and Ma⁶³ groups independently reported the use of *N*-(2-pyridyl)sulfonyl and 2-

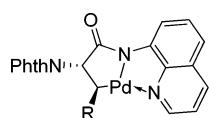
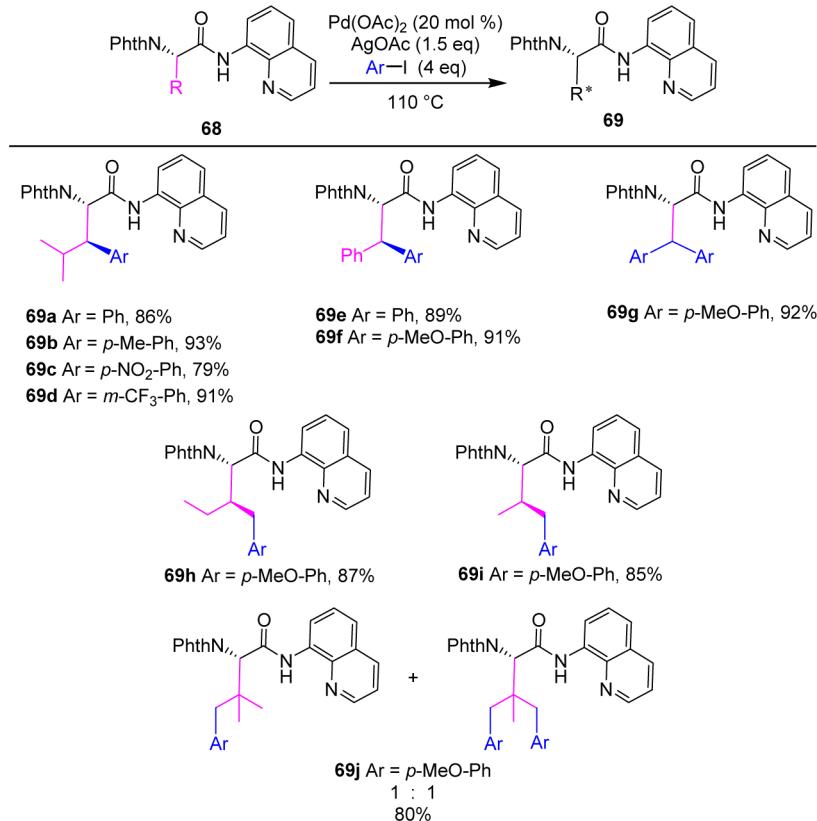
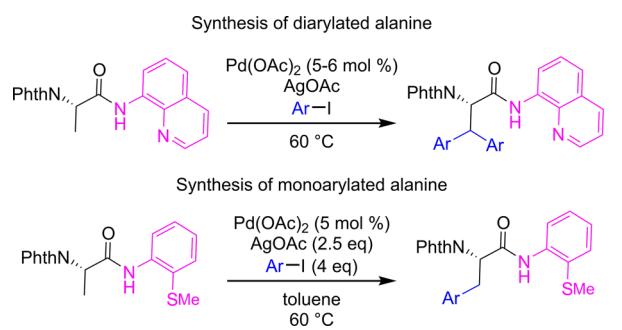
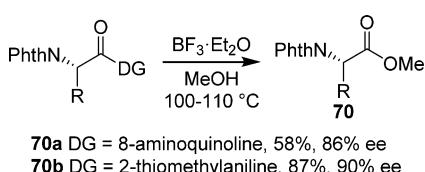
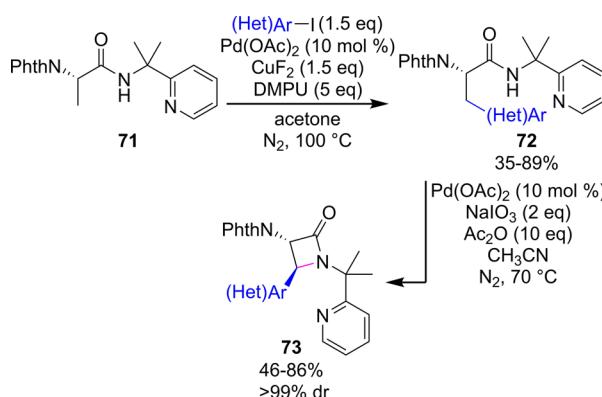
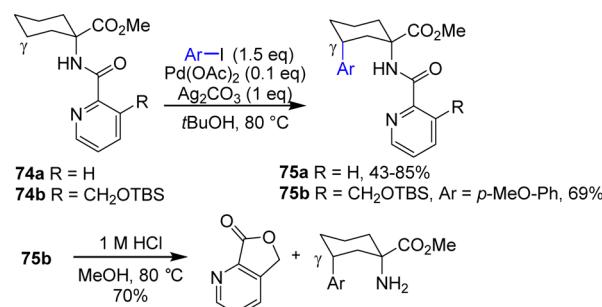
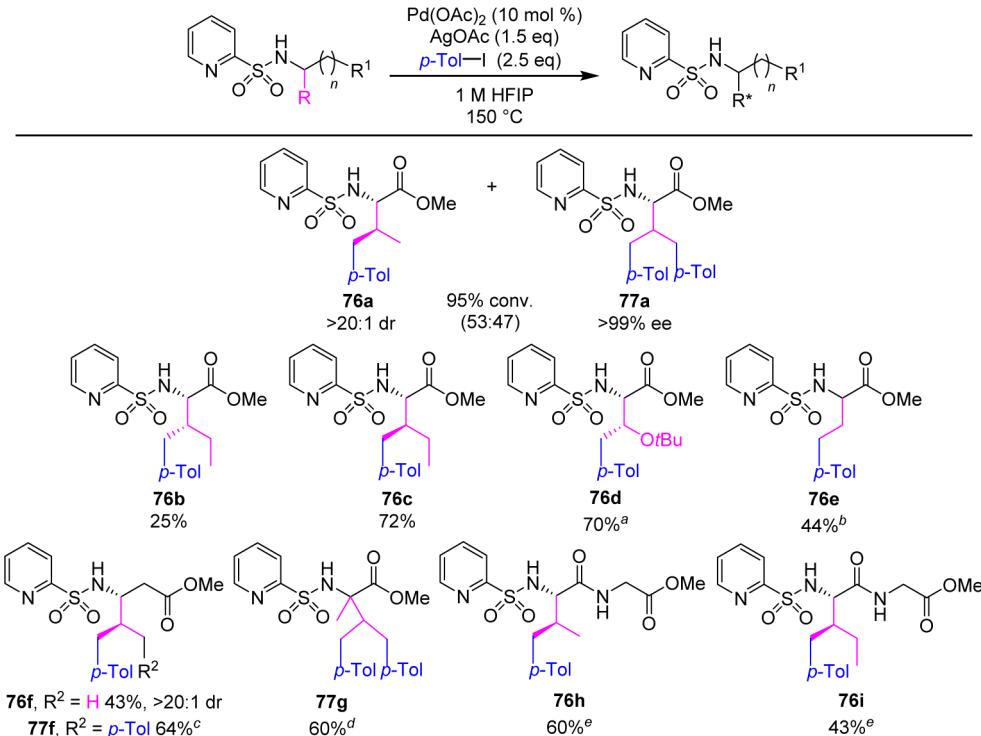


Figure 2. Structure of the double five-membered palladacycle formed with the 8-aminoquinoline DG.

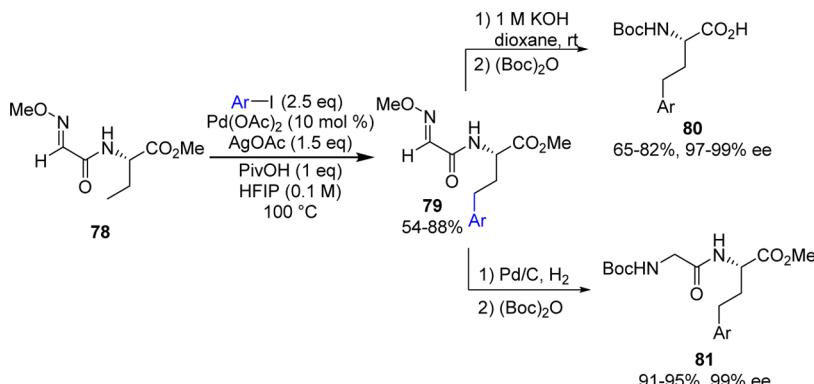
Scheme 30. Palladium-Catalyzed 8-Aminoquinoline-Directed C(sp³)–H Arylation of C(sp³)–H Bonds in Amino Acids⁵⁶**Scheme 31.** Synthesis of Mono- and Diarylated Alanine Derivatives by Changing the DG**Scheme 32.** DG Removal⁵⁹

methoxyiminoacetyl (MIA) auxiliaries for the γ -arylation of amino acids. The former group initially described the reaction of L-valine methyl ester bearing the *N*-(2-pyridyl)sulfonyl DG with 4-iodotoluene catalyzed by 10 mol % of Pd(OAc)₂ in the presence of AgOAc in hexafluoroisopropanol (HFIP) at 150 °C.⁶² The starting material was successfully converted in 95% yield affording a mixture of almost 1:1 γ -mono- and γ -bis-arylated products (**76a** and **77a**). Interestingly, the mono-arylated product was formed with a 20:1 diastereoisomeric ratio

Scheme 33. Palladium-Catalyzed Sequential Monoarylation/Amidation of C(sp³)–H Bonds⁶⁰**Scheme 34.** Picolinamide-Directed γ -Arylation of C(sp³)–H Bond⁶¹

Scheme 35. *N*-(2-Pyridyl)sulfonyl-Directed γ -Arylation of C(sp³)–H Bond^{62a}

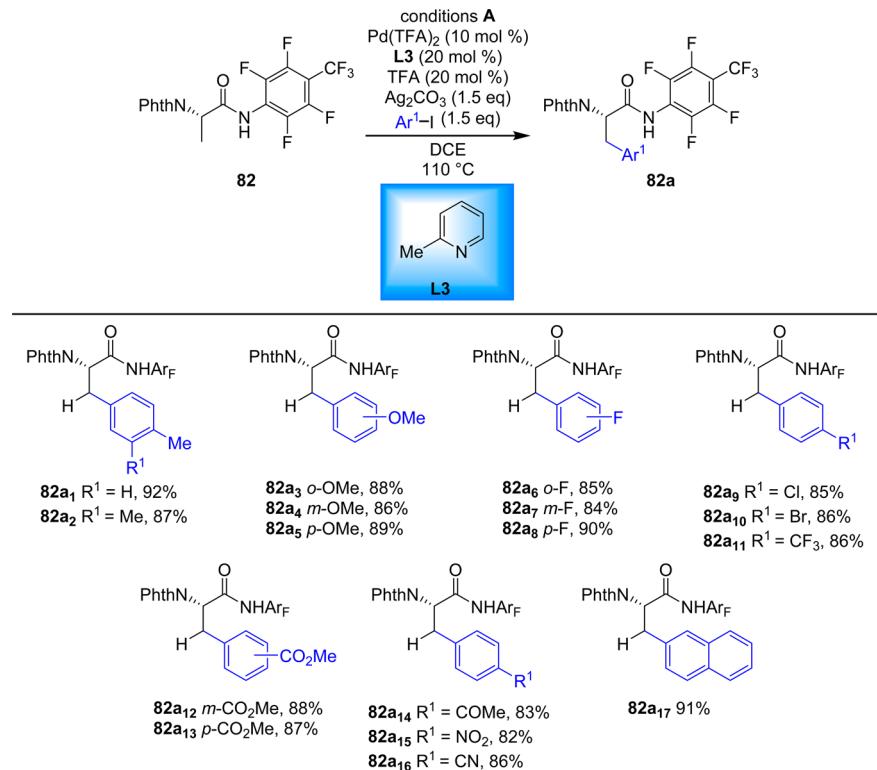
^a(a) 0.2 M HFIP at 120 °C; (b) Pd(OAc)₂ (20 mol %), AgOAc (3 equiv); (c) *p*-Tol-I (5 equiv), AgOAc (3 equiv); (d) *p*-Tol-I (3 equiv), AgOAc (2 equiv); (e) AgOAc (3 equiv).

Scheme 36. MIA-Directed γ -Arylation of C(sp³)–H Bond⁶³

(dr) in favor of 3S-76a. While both the conversion and the selectivity toward the bis-arylated compound 77a could be improved by increasing the equivalents of 4-iodotoluene, a more favorable ratio towards the formation of monoarylated product 76a (80:20) could be obtained either by decreasing the reaction temperature to 140 °C or by increasing the steric bulk of the iodoaryl reagent. Next, the scope of the reaction was investigated with regard to the amino acid precursor. Using isoleucine, allo-isoleucine, threonine, homoleucine, α -methylvaline, and β -homovaline, yields ranging from poor to good were obtained. Interestingly, while the arylation of isoleucine only afforded 77b in 25% yield, the reaction of its diastereoisomer yielded 77c in 72% yield. This remarkable difference in reactivity is believed to be the result of the accessibility of the palladium to the stereochemically different 1° C(sp³)–H bond. Furthermore, no arylation of 2° C(sp³)–H bonds was detected. The threonine, homoleucine, and β -homovaline analogues

afforded the desired monoarylated products 76d, 76e, and 76f in 70%, 44%, and 43% yield, respectively. The bis-arylated products 77f (64% yield) and 77g (60% yield) were obtained in the case of the β -homovaline and α -methylvaline analogues using 5 and 3 equivalents of 4-iodotoluene, respectively. Dipeptides valine-glycine and isoleucine-glycine were also good substrates for the reaction affording 76h and 76i in 60% and 43% yield, respectively, thus providing the first example of remote C–H arylation of dipeptides. Carretero's findings on the γ -arylation of C(sp³)–H bond are summarized in Scheme 35.

The influence of the electronic properties of the iodoaryl coupling partners was also evaluated. Good yields were obtained with both electron-donating and electron-withdrawing substituents. The *N*-(2-pyridyl)sulfonyl DG was successfully removed by treatment with Zn/NH₄Cl, affording the free amine methyl ester in excellent ee.

Scheme 37. Ligand-Controlled Monoarylation of 1° C(sp³)–H Bond with Pyridine-Based Ligand L3⁶⁴

On the other hand, Ma and co-workers achieved the C–H γ -arylation reaction of homoalanine methyl ester bearing the MIA DG 78 with 4-iodoanisole and PivOH as an additive in 67% yield, using mild and dilute reaction conditions.⁶³ A broad range of aryl iodides were reacted, which afforded the desired homophenylalanine derivatives 79 in good yields. The MIA group was either removed by hydrolysis with 1 M KOH thus affording the free amine, which after Boc protection gave 80, or transformed to a glycine moiety upon hydrogenation yielding dipeptide 81 after Boc protection, as depicted in Scheme 36. Next, the reaction was successfully extended to the valine, threonine, allo-isoleucine, and α -methylhomoalanine analogues.

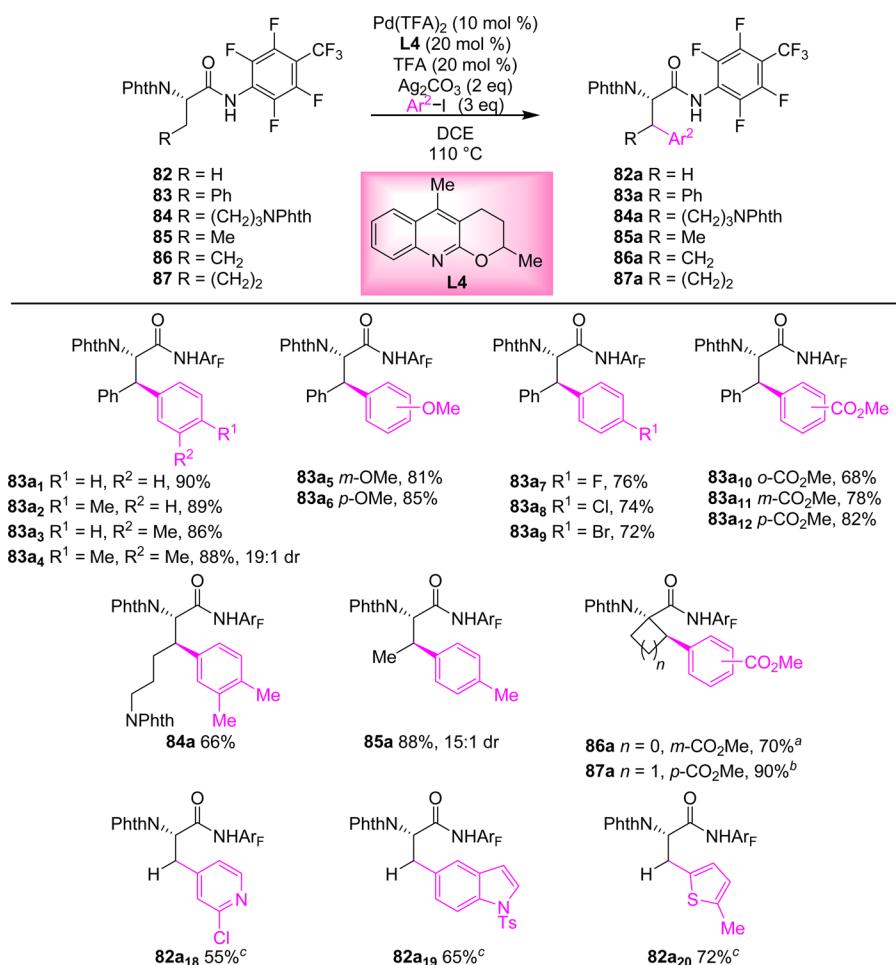
Recently, the Yu group reported the first example of ligand-controlled C(sp³)–H arylation of amino acids.⁶⁴ This technique allows the fine-tuning of reactivity and selectivity of transition-metal catalysts for C(sp³)–H bond functionalization. Using N-phthaloyl alanine 82 bearing the weakly coordinating 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline auxiliary in conjunction with various pyridine- and quinoline-based ligands, they achieved the sequential one-pot C–H diarylation affording hetero- β,β' -diarylated products 82b (see Scheme 39, *vide infra*). While pyridine-based ligands were found to promote the selective monoarylation of the 1° C(sp³)–H bond with aryl iodides, quinoline-based ligands catalyzed the subsequent arylation of the newly formed 2° C(sp³)–H bond with distinct aryl iodides. Among the various pyridine-based ligands tested, ligand L3 provided the optimal balance between yield and mono- versus diarylation selectivity and was therefore examined in the monoarylation of 82 with a wide range of aryl iodides. Using reaction conditions A, 10 mol % Pd(TFA)₂, 20 mol % TFA, Ag₂CO₃ (1.5 equiv), Ar–I (1.5 equiv) in 1,2-dichloroethane (DCE) at 100 °C, compounds 82a_{1–17} were prepared in good yields from aryl iodides bearing both electron-with-

drawing and electron-donating substituents; however, reactions with heteroaryl iodides were unsuccessful (Scheme 37).

Quinoline ligand L4 was, in turn, designed to promote 2° C(sp³)–H arylation of phenylalanine derivative 83 with aryl iodides. Again, the reaction was tolerant to both electron-withdrawing and electron-donating substituents, and using reaction conditions B, 10 mol % Pd(TFA)₂, 20 mol % TFA, Ag₂CO₃ (2 equiv), Ar–I (3 equiv) in DCE at 100 °C, compounds 83a_{1–12} were prepared in synthetically useful yields with excellent diastereoisomeric ratios. Interestingly, despite the steric hindrance, the reaction with *ortho*-substituted aryl iodide proceeded to afford 83a₁₀ in 68% yield. In addition to phenylalanine, the C–H arylation of lysine (84), homoalanine (85), 1-aminocyclobutane-1-carboxylic acid (86), and 1-amino-cyclopropane-1-carboxylic acid (87) derivatives were investigated. The resulting compounds 84a–87a were isolated in yields ranging from 66% to 90% yields. Although ligand L4 failed to promote the arylation of 83 with heteroaryl iodides, it was found to catalyze the monoarylation of alanine 82 with pyridyl-, indolyl-, and thiophenyl iodides, yielding products 82a_{18–20} in 55%, 65%, and 72% yield, respectively (Scheme 38).

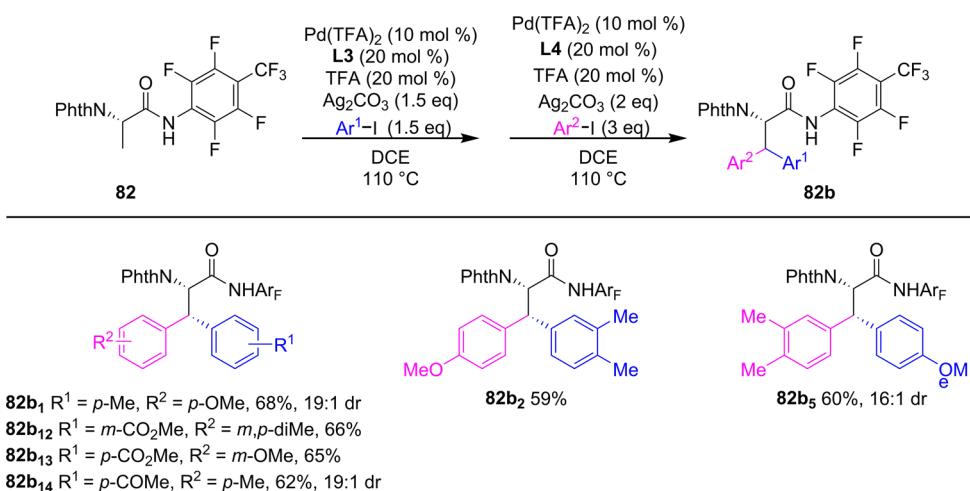
Finally, hetero- β,β' -diarylated products 82b₁, 82b_{12–14} were successfully prepared by reacting 82 with *p*-Me, *m*-CO₂Me, *p*-CO₂Me, and *p*-COMe-substituted aryl iodides under reaction conditions A, thus yielding compounds 82a₁ and 82a_{12–14}, which were subsequently subjected to 2° C(sp³)–H arylation under reaction conditions B with *p*-OMe, *m,p*-diMe, *m*-OMe, and *p*-Me-substituted aryl iodides, respectively. Furthermore, the opposite stereochemistry could be obtained at the β -stereogenic center by simply switching around the order of addition of the different aryl iodides, as exemplified by the preparation of the (S,S)-82b₂ and (S,R)-82b₅ diastereoisomers (Scheme 39).

Scheme 38. Ligand-Controlled Arylation of 2° C(sp³)–H Bond and Monoheteroarylation of 1° C(sp³)–H with Quinoline-Based Ligand L4^{64a}



^a≥20:1 dr unless otherwise stated. (a) Yield for mixture of mono:diarylated compounds (>20:1), single diastereoisomers; (b) yield for mixture of mono:diarylated compounds (2:1), single diastereoisomers; (c) Pd(TFA)₂ (15 mol %), L4 (30 mol %), Ag₂CO₃ (2 equiv), and HetAr-I (1.5 equiv).

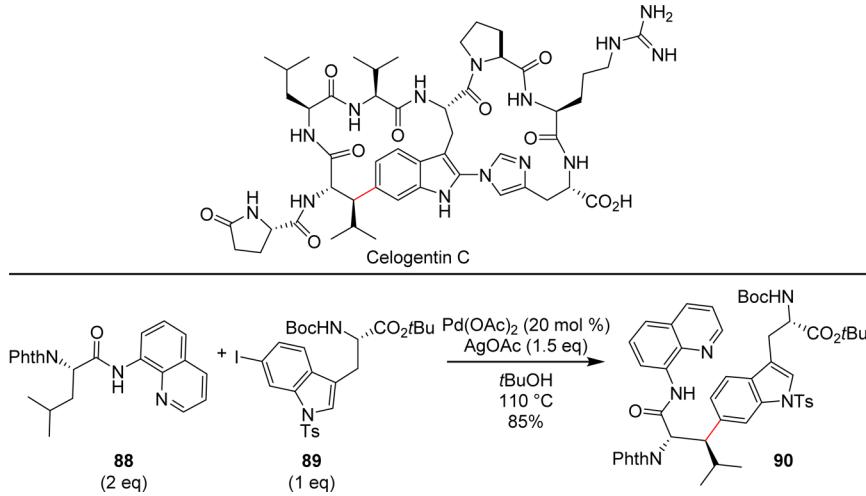
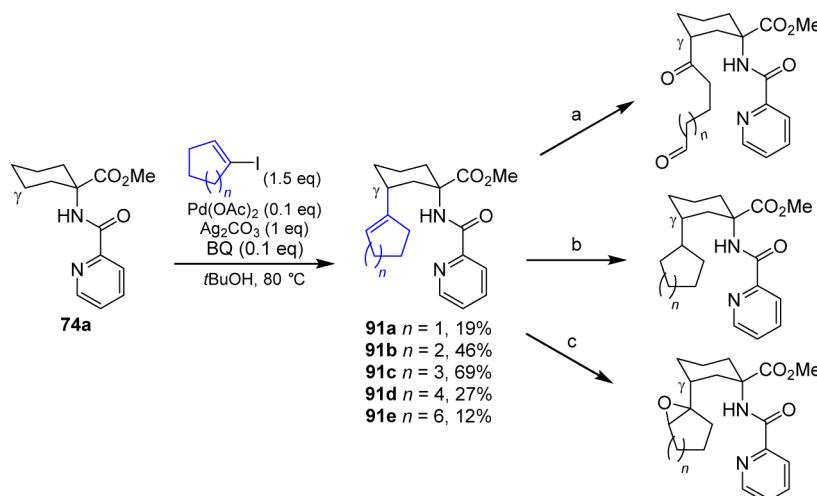
Scheme 39. Ligand-Controlled Sequential One-Pot C–H Diarylation of C(sp³)–H Bond^{64a}



^a(a) ≥20:1 dr unless otherwise stated.

The utility of the C(sp³)–H arylation reaction in natural product synthesis was demonstrated by Feng and Chen who employed the palladium-catalyzed C–H arylation as a key step for their synthesis of Celogentin C.⁶⁵ Celogentin C is a natural

bicyclic peptide inhibitor of tubulin polymerization, which presents a rare linkage between the β-C(sp²) of the leucine and the position C6 of the aryl ring of the tryptophan residue. The key motif **90** was obtained in 85% yield with complete

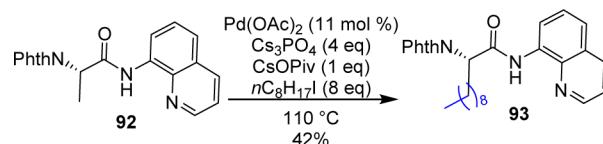
Scheme 40. Key Pd-Catalyzed C(sp³)–H Arylation Step in the Synthesis of Celogentin C⁶⁵Scheme 41. PA-Directed γ -Alkenylation of C(sp³)–H Bond⁶¹

diastereoselectivity from the coupling of the N-phthaloyl leucine bearing the 8-aminoquinoline DG 88 and the protected 6-iodotryptophan 89 as depicted in Scheme 40.

2.3.3. Alkenylation. In addition to γ -arylation, He and Chen also reported the PA-directed remote γ C(sp³)–H alkenylation of cyclohexylamino acid 74a with various disubstituted cyclic vinyl iodides.⁶¹ The alkenylated products 91 were obtained in poor to good yields, which appeared to be greatly influenced by the size of the ring. Such products represent valuable intermediates en route to (a) acylated, (b) alkylated, or (c) epoxidized amino acids through ozonolysis, hydrogenation, or oxidation, respectively (Scheme 41).

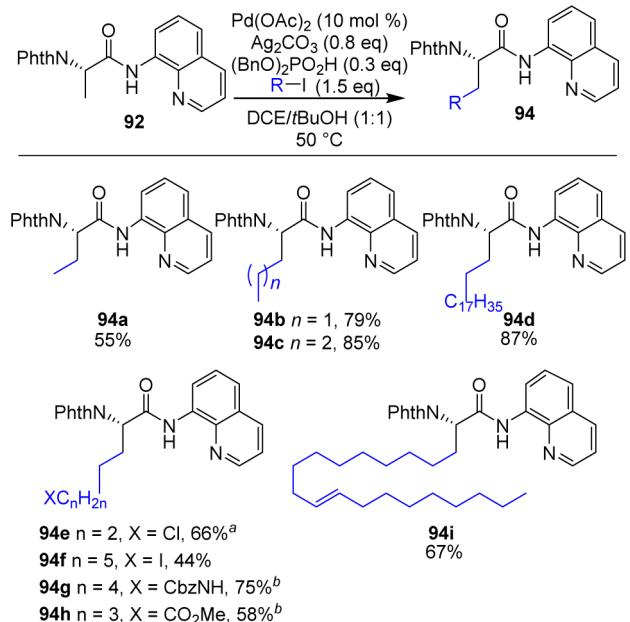
2.3.4. Alkylation. The first example of alkylation of amino acids through C(sp³)–H bond activation was reported by Daugulis et al.⁵⁹ who successfully reacted N-phthaloylalanine derivatized with the 8-aminoquinoline DG 92 with 1-iodooctane. Using 11 mol % of Pd(OAc)₂ as well as a combination of Cs₃PO₄ and CsOPiv bases at 110 °C, the desired alkylated product 93 was obtained in 42% yield (Scheme 42).

Inspired by the work of Chen⁶⁶ on the use of (BnO)₂PO₂H as a solid to solution phase-transfer catalyst for Ag₂CO₃ and the early efforts of Daugulis,⁵⁹ the Shi group recently reported mild conditions for the alkylation of 92 with *n*-iodobutane.⁶⁷

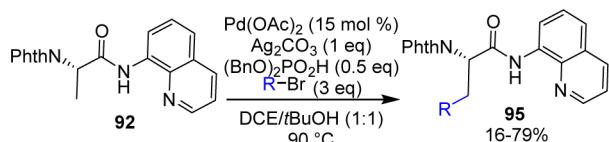
Scheme 42. Daugulis' β -Alkylation of 1° C(sp³)–H Bond⁵⁹

Screening of various halide scavengers and additives showed that the use of silver salts together with (BnO)₂PO₂H critically improved the reaction yield; thus the desired compound 94c could be isolated in 85% yield as depicted in Scheme 43.

The Ag⁺ cations may not only act as halide scavengers necessary for high turnover of the catalytic cycle, but also their Lewis acidity might enhance the electrophilicity of the alkyl iodides. On the other hand, increased concentration of Ag⁺ might lead to decomposition of the alkyl iodides through E2 elimination. The (BnO)₂PO₂H additive was proposed to enable a better control of the concentration of Ag⁺ in solution, thus playing a key role in the oxidative addition step. Shi's optimized reaction conditions promoted the coupling of a wide range of primary alkyl iodides, encompassing various size alkyl chains from methyl iodide to C₁₈H₃₇I yielding products 94a–d in good to high yields.⁶⁷ Alkyl iodides bearing functional groups

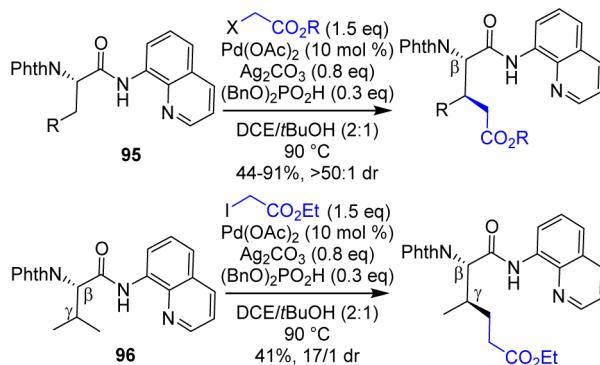
Scheme 43. Shi's β -Alkylation of 1° C(sp³)–H Bond^{67a}

such as halides, protected amines, carboxylic esters, and alkenes were also reacted, successfully affording compounds 94e–i (Scheme 43). It should be noted that the more hindered secondary alkyl iodides remained unreactive. Interestingly, the C(sp³)–H alkylation with alkyl bromide coupling partners also took place, and good yields of the alkylated products 95 could be obtained albeit requiring slightly harsher conditions (Scheme 44).⁶⁷ This represents the first example of C(sp³)–H alkylation with alkyl bromides.

Scheme 44. Pd-Catalyzed β -Alkylation of 1° C(sp³)–H Bond Using Alkyl Bromides⁶⁷

In addition, the Shi group also reported the alkylation of the β -2° C(sp³)–H bond of various amino acid derivatives with α -iodoacetate esters and α -bromoacetate esters.⁶⁷ Finally, in the absence of 1° or 2° C(sp³)–H bond in β -position, γ -alkylation took place, thus providing the first example of C(sp³)–H alkylation directed through a six-membered ring palladacycle. The β -carbomethylation of the 2° C(sp³)–H bond of 95 as well as the γ -carboxylation of the 1° C(sp³)–H bond of 96 are represented in Scheme 45.

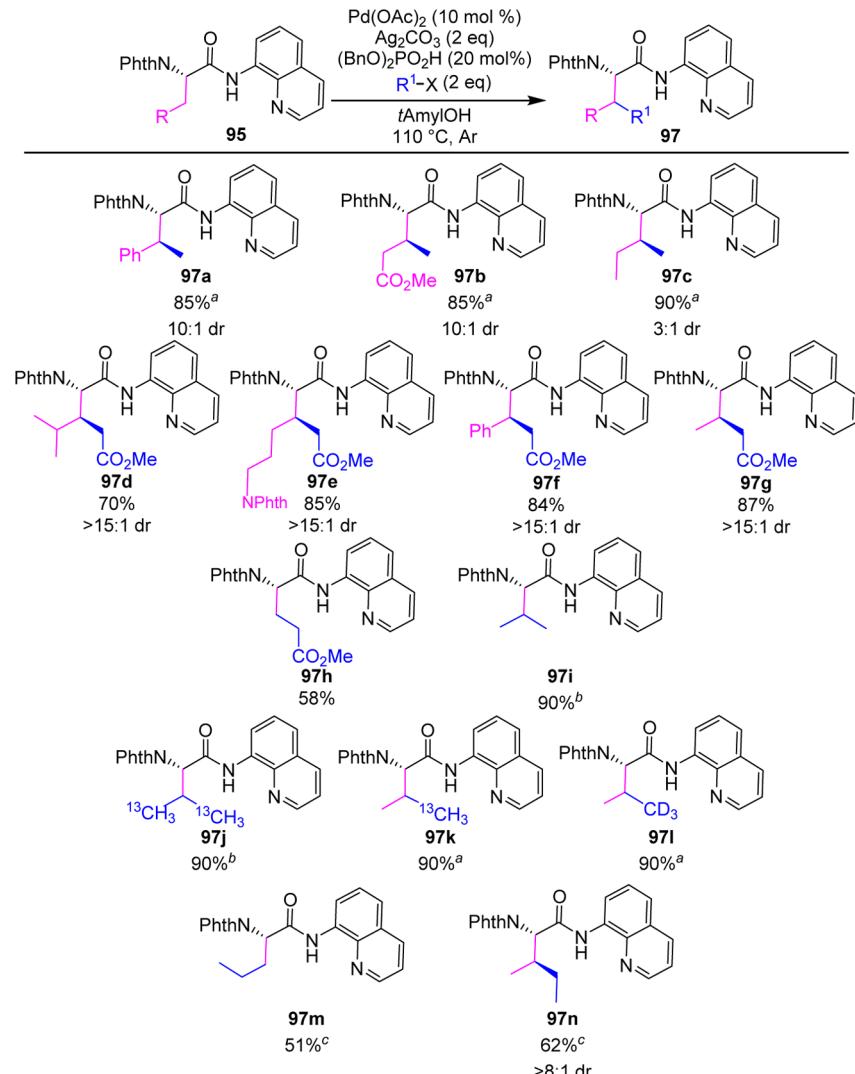
Independently from the work of Shi,⁶⁷ Chen reported the mono- β -methylation of 2° C(sp³)–H bonds of phenylalanine, glutamic acid, and norvaline derivatives yielding compounds 97a–c and the monocarboxymethylation of leucine, lysine, phenylalanine, and homoolanine derivatives yielding compounds 97d–g with good yields and diastereoselectivity.⁶⁸ The alanine derivative was monocarboxylated when haloacetate was used, affording 97h in 58% yield. However, using 2.2 equiv

Scheme 45. β -Alkylation of 2° C(sp³)–H Bond and γ -Alkylation of 1° C(sp³)–H Bond⁶⁷

of methyl iodide, valine 97i was obtained in 90% yield from bismethylation. Isotope-labeled methyl iodide was also employed to afford isotope-enriched amino acids 97j–l. The less reactive ethyl iodide also reacted under the same reaction conditions; however, poorer yields were obtained for the ethylation reaction, yielding 97m and 97n in 51% and 62% yield, respectively. Additionally, Chen demonstrated that both diastereoisomers of the β -branched amino acids were available by simply reversing the C–H alkylation sequence.⁶⁸ The work of Chen is summarized in Scheme 46.

In conclusion, although the discovery of 2° C(sp³)–H alkylation is of considerable importance because the alkylation of methylene C(sp³)–H is rare in the literature, the scope of alkyl halides that can be employed remain limited to activated halides such as methyl iodide, α -iodoacetate esters, and α -bromoacetate esters; thus many challenges remain to be addressed to render the reaction widely applicable.

2.3.3.5. Borylation. Recently, the challenging palladium C(sp³)–H borylation of PA-directed amino acids has been reported by Zhang et al.³⁶ Although borylated compounds are particularly important precursors en route to more complex products via Miyaura–Suzuki coupling, this same reactivity has hampered the development of palladium-catalyzed C–H borylation reactions. Additional difficulties lay in the propensity of the alkyl boronate ester formed to be oxidized in the presence of the stoichiometric oxidant necessary for the completion of the Pd-catalytic cycle. Thanks to an extensive screening of catalysts, ligands, oxidants, bases, solvents, and additives, the conditions summarized in Scheme 47 were identified, which afforded the desired product 98a from the mono- γ -borylation of valine in good yield with good dr (68% yield, 83:17 dr). iPr₂S was found to be a good ligand to prevent the precipitation of the catalyst to palladium black. Furthermore, the weak base Li₂CO₃ was found to promote the formation of the desired borylated product without enhancing its reactivity toward Suzuki side-reactions. Interestingly, while other oxidants failed, using O₂ as the sole oxidant allowed the regeneration of the palladium catalyst. The scope of the reaction was next investigated using these optimized conditions. Isoleucine, *tert*-leucine, and *O*-*tert*-butyl threonine were mono- γ -borylated to afford products 98b, 98c, and 98d, respectively, in good yields (70%, 61%, and 84% yield, respectively). The reaction conditions were also applied to the functionalization of aromatic amino acids. Notably, the γ -C(sp²)–H borylation of arylglycine afforded the *ortho*-borylated compound 98e in 82% yield, while in phenylalanine, due to the absence of C(sp²)–H bond γ of the amine, the

Scheme 46. β -Methylation and β -Carboxymethylation of 2° C(sp³)–H Bond^{68a}

^a(a) MeI (1.1 equiv); (b) MeI (2.2 equiv); (c) EtI (3 equiv), Ag₂CO₃ (1 equiv).

activation of the δ -C(sp²)–H bond provided product **98f** in 63% yield.

3. C–H FUNCTIONALIZATION VIA CARBENOID INTERMEDIATES

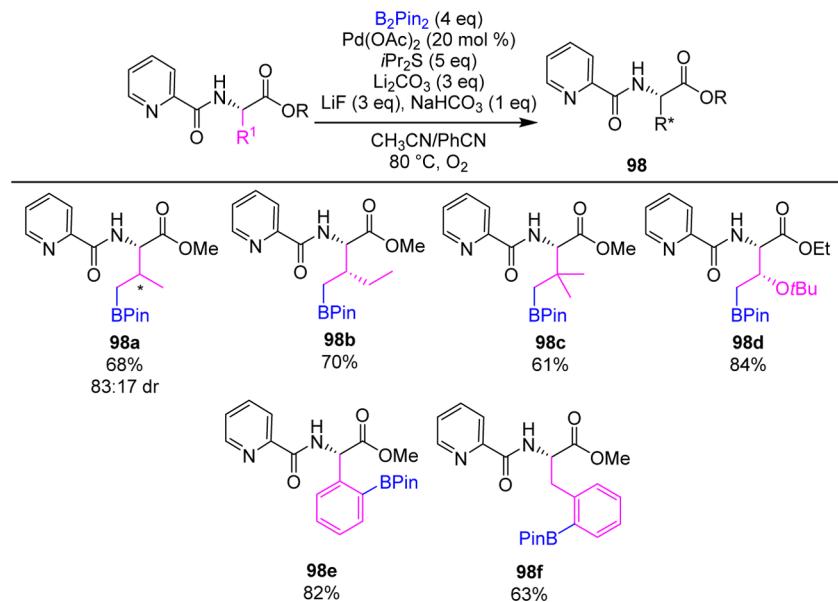
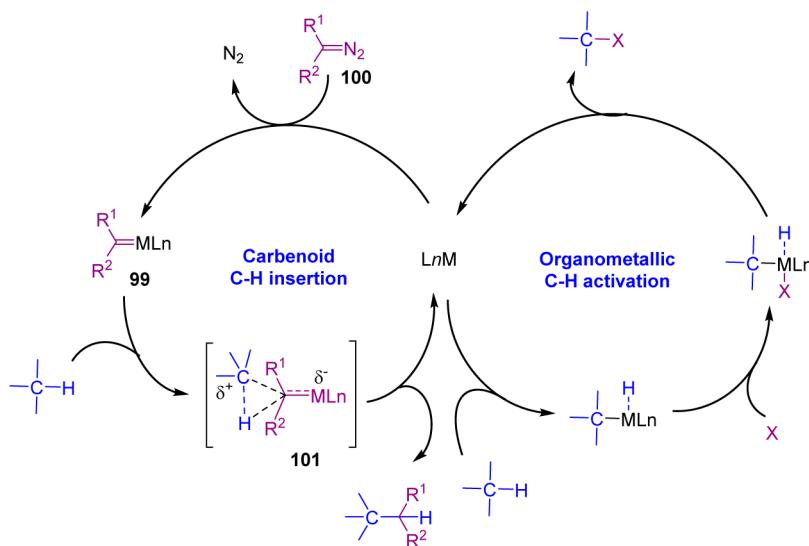
3.1. Background

Although often excluded from reviews on C–H functionalization, the metal–carbenoid induced C–H functionalization strategy belongs to the transition metal-catalyzed C–H functionalization category and is an area of active research.⁶⁹ Scheme 48 represents the difference between the organometallic C–H functionalization method, which involves an inner-sphere mechanism, and the C–H insertion of carbenoids, which follows an outer-sphere mechanism. In the latter case, the metal atom does not interact directly with the C–H bond. The carbenoid intermediates **99** are commonly accessed from the metal-assisted decomposition of diazo compounds **100**. In contrary to traditional transition metal-catalyzed C–H functionalization, the metal–carbenoid induced C–H functionalization catalytic cycle is therefore extremely favorable.

Carbenoid C–H functionalization long remained limited to intramolecular reactions; however, the use of carbenoids bearing both an EWG and an EDG has allowed for the development of efficient intermolecular reactions. The regioselectivity of the reaction differs from that of the organometallic C–H activation, with the insertion within 3° C(sp³)–H bonds being electronically more favorable. In the transition-state **101**, the carbon undergoing the C–H functionalization builds up a positive charge; thus, carbons adjacent to functionalities that are able to stabilize the positive charge are the more electronically favored. Steric effects also contribute to explain the regiocontrol. Common substrates for the carbenoid insertion are C–H bonds of methines and methylenes. C–H bonds α to heteroatoms, as well as allylic and benzylic positions, also are activated sites reacting in good regioselectivity. In terms of enantioselectivity, the use of chiral catalysts affords product in high ee.

3.2. C–H Functionalization in Amino Acids

In 2002, Davies et al.⁷⁰ published the synthesis of β_2 -amino acids based on the intermolecular rhodium-carbenoid insertion in *N*-protected methylamines, thus providing the first report of selective insertion into a 1° C(sp³)–H bond. Using [Rh₂(S-

Scheme 47. Palladium-Catalyzed PA-Directed Borylation of C(sp³)—H and C(sp²)—H Bonds³⁶**Scheme 48.** Outer-Sphere versus Inner-Sphere Type Mechanism

DOSP)₄] in 2,2-dimethylbutane, various *N*-protected methylamines **102** were examined for the reaction with aryl diazoacetate **103**; among them, *N*-Boc-*N*-methyl benzylamine **102e** gave the best results in terms of yield and ee (62% yield, 95% ee). Substituted phenyldiazoacetates but also 2-naphthyl diazoacetate, 3-thienyl diazoacetate, and styryldiazoacetate were successfully reacted with **102e** in good yields and good to excellent ee (Scheme 49).

Thanks to its different reactivity, the metal-catalyzed carbenoid C–H insertion technique brings an additional diversity to the traditional organometallic C–H functionalization strategy, providing access to β_2 -amino acids in an enantioselective fashion.

4. C–H FUNCTIONALIZATION VIA IONIC INTERMEDIATES

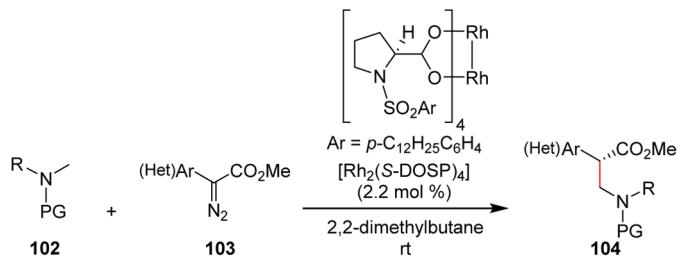
4.1. Background

Another strategy for the formation of C–C bonds via C–H functionalization consists of generating an electrophile in situ by transition-metal catalyzed abstraction of a proton under oxidative conditions. The electrophile thus formed subsequently reacts with a nucleophilic species.

4.2. C–H Functionalization in Amino Acids and Peptides

Li et al.⁷¹ reported the C(sp³)–H arylation of *N*-para-methoxybenzyl (*N*-PMP) glycine amide derivatives **105** with aryl-, heteroaryl-, and vinylboronic acids as nucleophiles, using CuBr as catalyst and *tert*-butyl hydroperoxide (TBHP) as oxidant in chlorinated solvents (Scheme 50).

While a wide scope of boronic acids afforded the desired coupling products (**106a–d** and **106g–i**) in good yields, coupling with arylboronic acids bearing strongly EWGs failed to

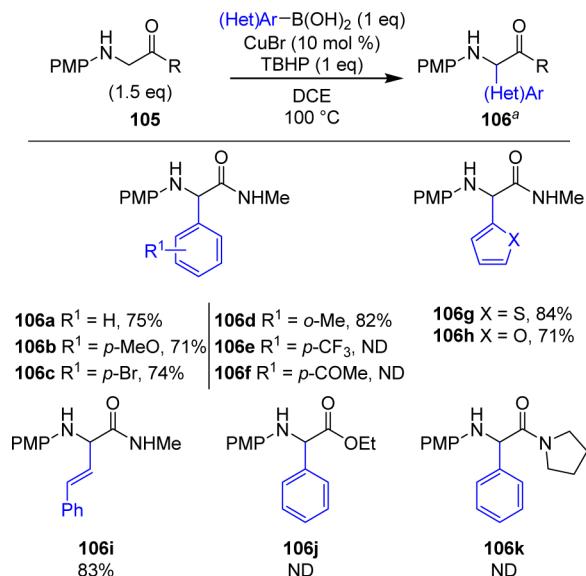
Scheme 49. Asymmetric Synthesis of β_2 -Amino Acids by Rhodium–Carbenoid C–H Insertion⁷⁰

Reaction of 103a (Het)Ar = 4-Br-Ph with :

- 102a PG = Boc, R = Me \rightarrow 104a 61%, 31% ee
 102b PG = Boc, R = nPr \rightarrow 104b 46%, 64% ee
 102c PG = Boc, R = iPr \rightarrow 104c 57%, 82% ee
 102d PG = Boc, R = tBu \rightarrow 104d 58%, 54% ee
 102e PG = Boc, R = Bn \rightarrow 104e 62%, 95% ee
 102f PG = Boc, R = (CH₃)₂C=CHCH₂
 \rightarrow 104f 62%, 87% ee
 102g PG = Boc, R = trans-PhC=CHCH₂
 \rightarrow 104g 60%, 87% ee
 102h PG = Fmoc, R = Bn \rightarrow 104h 21%, 69% ee
 102i PG = Cbz, R = Bn \rightarrow 104i 67%, 90% ee
 102j PG = Teoc, R = Bn \rightarrow 104j 26%, 94% ee

Reaction of 102e PG = Boc, R = Bn with :

- 103b (Het)Ar = Ph \rightarrow 104k 67%, 96% ee
 103c (Het)Ar = 4-CF₃-Ph \rightarrow 104l 55%, 92% ee
 103d (Het)Ar = 4-OMe-Ph \rightarrow 104m 61%, 92% ee
 103e (Het)Ar = 4-Me-Ph \rightarrow 104n 66%, 95% ee
 103f (Het)Ar = 4-Cl-Ph \rightarrow 104o 62%, 96% ee
 103g (Het)Ar = 4-CH=CH₂-Ph \rightarrow 104p 56%, 96% ee
 103h (Het)Ar = 2-naphthyl \rightarrow 104q 55%, 87% ee
 103i (Het)Ar = 3-thienyl \rightarrow 104r 58%, 90% ee

Scheme 50. α -Arylation of N-PMP Glycine Derivatives^{71a}^a(a) Isolated yields are based on boronic acid starting materials.

provide compounds 106e,f. Interestingly, neither N-PMP glycine esters nor N-PMP glycines exhibiting a tertiary amide proved to be reactive substrates when treated with phenylboronic acid under the previously established reaction conditions. Thus, the formation of the expected compounds 106j and 106k, respectively, was not observed.

However, using dipeptides and tripeptides 107 as substrates, the desired monoarylated products 108 were obtained in good yields, and no trace of arylation of other residues except the N-terminal amino acid was detected, thus demonstrating the direct and selective α -functionalization of simple peptides (Scheme 51). Some diastereoselectivity was observed, which appears to be independent of the position of the existing stereocenter; furthermore, under these oxidative reaction conditions, no racemization of the existing chiral center occurred.

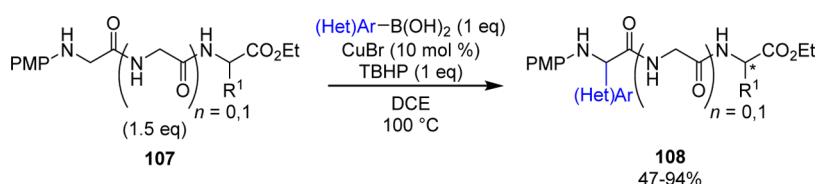
Li et al.⁷¹ proposed a plausible reaction mechanism, which is in accordance with the observed reactivity. First, the glycine derivative 105 undergoes oxidative dehydrogenation to the imino amide intermediate 109. The tautomeric iminol form 110 coordinates with the boronic acid, thus increasing the nucleophilicity of the phenyl group, which undergoes nucleophilic addition to the imine bond and affords the desired α -arylated compound 111 after final hydrolysis (Scheme 52).

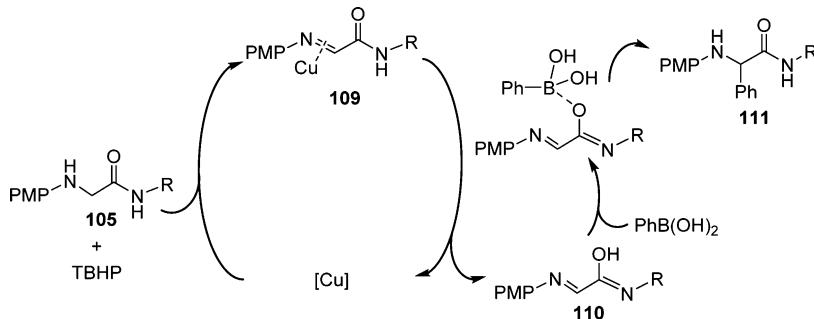
The copper-catalyzed oxidation to the imine is believed to proceed through H-abstraction and single-electron transfer (SET) mechanisms as depicted in Scheme 53; therefore, the reaction could also be classified as C–H functionalization via radical intermediates.

5. CROSS-DEHYDROGENATIVE COUPLING VIA ORGANOMETALLIC INTERMEDIATES

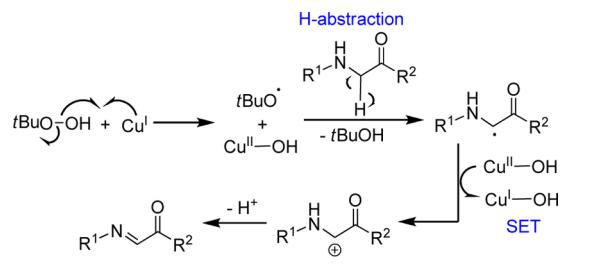
5.1. Background

With the increasing concerns for environmental issues, chemists are continually trying to develop reactions with low economic

Scheme 51. α -Arylation of N-PMP Glycine Di- and Tripeptides⁷¹

Scheme 52. Proposed Mechanism for the α -Arylation of N-PMP Glycine Amide⁷¹

Scheme 53. Formation of the Imine Electrophile through Copper-Catalyzed Oxidation



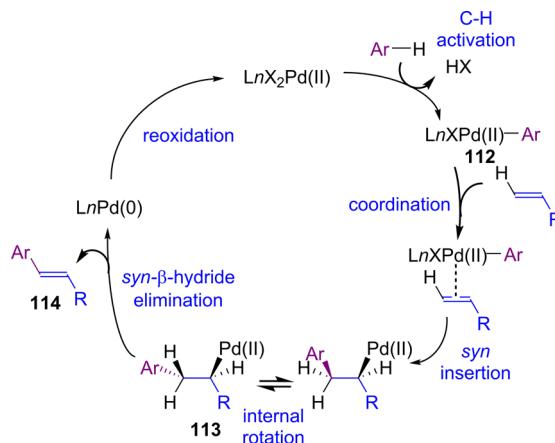
and ecological impacts. Unlike C–H functionalization reactions, which still involve one prefunctionalized coupling partner, CDC reactions allow the formation of C–C bonds directly from two different C–H bonds under oxidative conditions. In the realm of green chemistry, CDC has attracted considerable attention as it ideally eliminates unwanted wastes and considerably shortens the synthetic routes. However, to proceed, CDC reactions usually require the use of high loading of transition-metal catalysts and sacrificial oxidants. The two most common CDC reactions involving organometallic intermediates are the tandem direct arylation between two C(sp²)–H bonds of arenes and the Fujiwara–Moritani reaction, which involves the olefination of an arene following a Heck-type mechanism.^{18a} Coupling between two olefins is rarest, due to the dominance of the homocoupling side-reaction. Finally, a few examples of palladium-catalyzed CDC reactions between C(sp²)–H and C(sp³)–H bonds have appeared; nevertheless, this type of cross-dehydrogenative coupling is still in its infancy. For these couplings, palladium salts have been used as the catalysts of choice; however, other transition metals such as rhodium, ruthenium, and iridium have also been employed with success. Palladium-catalyzed CDC coupling of C(sp²)–H bonds has been recently reviewed by Wu et al.⁷²

The catalytic cycle of the Fujiwara–Moritani reaction is depicted in Scheme 54. In a first step, the Pd(II) is selectively inserted in the C(sp²)–H bond of the arene, thus forming the organometallic intermediate 112, which coordinates and subsequently inserts into the C=C bond. An internal rotation following the syn-insertion step affords the intermediate 113, which undergoes syn-β-hydride elimination to release the alkene 114 and Pd(0). Finally, the Pd(II) active species is regenerated during a reoxidation step, which closes the catalytic cycle.

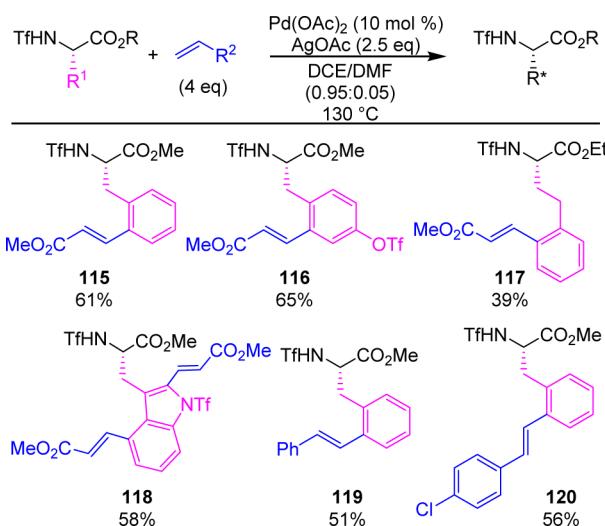
5.2. Cross-Dehydrogenative Coupling in Amino Acids

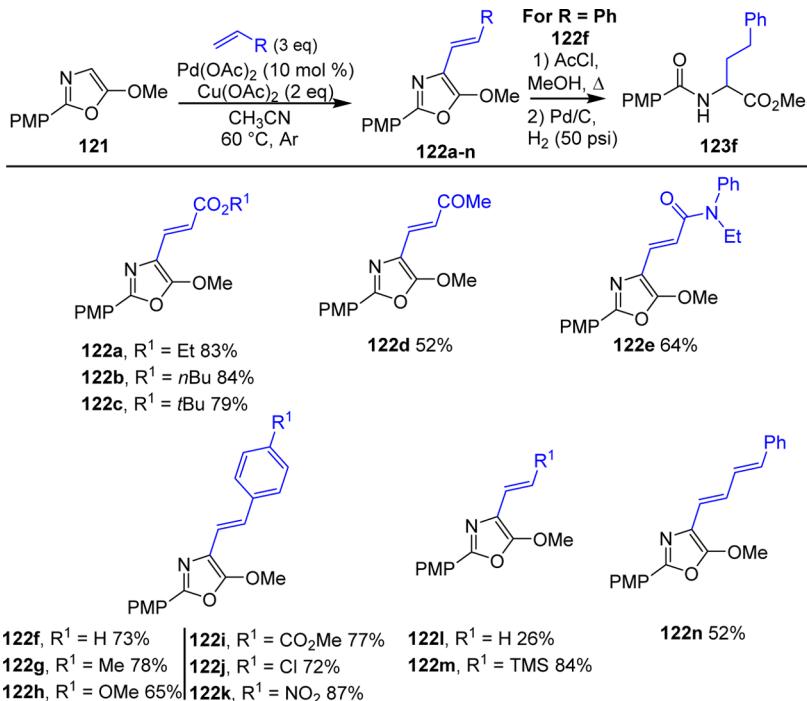
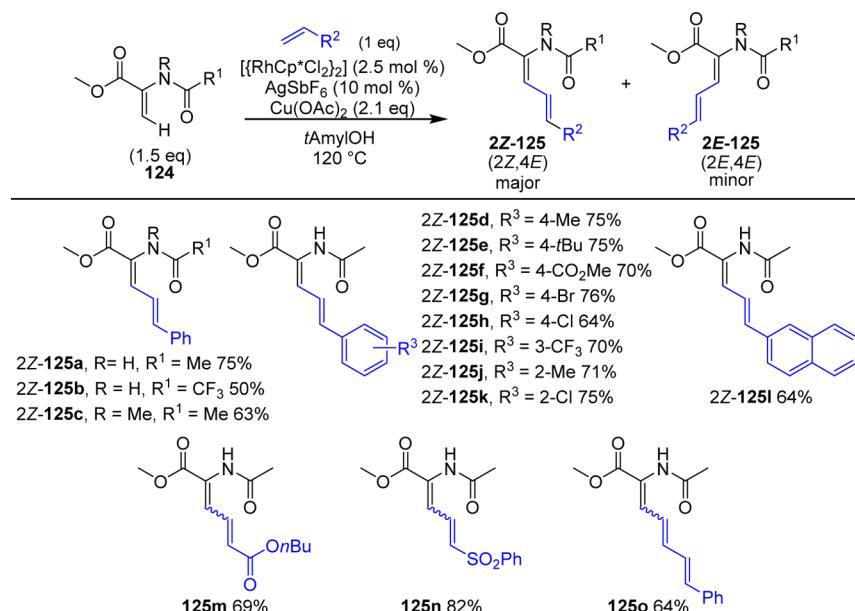
Although organometallic CDC reactions have attracted considerable attention, their application to amino acid synthesis

Scheme 54. Fujiwara–Moritani Reaction Catalytic Cycle



remains limited. An interesting contribution to the field was made by the Yu group, who described the triflamine-directed olefination of various N-triflamine methyl ester protected amino acids using Pd(OAc)₂ as a catalyst and AgOAc as the terminal oxidant (Scheme 55).⁴¹ Phenylalanine, homophenylalanine, and tyrosine derivatives were monoalkenylated with methyl acrylate affording products 115–117 in 61%, 65%, and 39% yield, respectively. The dialkenylation products were also isolated in less than 20% yield. The tryptophan derivative, however, afforded the 2,4-dialkenylated product 118 in 58%

Scheme 55. Alkenylation via Palladium-Catalyzed CDC Reaction⁴¹

Scheme 56. Introduction of the Side-Chain via Palladium-Catalyzed Alkenylation of Oxazole⁷³Scheme 57. Synthesis of Amino Acids through Rh-Catalyzed Olefination of Alkenes⁷⁴

yield. Other alkenes such as styrene and *para*-chlorostyrene also successfully reacted to give products **119** and **120** in moderate yields (51% and 56% yield, respectively).

Antilla and co-workers developed another approach making use of the Fujiwara–Moritani reaction for the synthesis of amino acids.⁷³ Unlike Li et al.,⁴¹ who employed the reaction to functionalize aromatic amino acid side-chains, Antilla and co-workers used the reaction to introduce the side-chain into a masked glycine template. Their strategy relies on the palladium-catalyzed alkenylation of an oxazole scaffold, followed by opening of the oxazole by hydrolysis and subsequent hydrogenation to afford racemic amino acids (Scheme 56). Initially, optimization of the reaction conditions for the

alkenylation of **121** with butyl acrylate, 10 mol % of $\text{Pd}(\text{OAc})_2$ with $\text{Cu}(\text{OAc})_2$ in DMF, was conducted, affording the desired product **122b** in 30% yield. Switching the solvent to CH_3CN slightly improved the yield (45% yield). However, decreasing the temperature from 70 to 60 °C and conducting the experiment under a flow of argon prevented olefin decomposition and thus led to an improved yield of 84%. Screening of various oxidants showed that neither AgOAc nor *p*-benzoquinone (BQ) was efficient. Attempts to replace CH_3CN for dimethyl sulfoxide (DMSO), DMF-DMSO cosolvent, or AcOH failed. Furthermore, neither adding pyridine as a ligand nor NaHCO_3 as a base improved the yield. The optimized reaction conditions shown in Scheme 56

were employed to investigate the reaction scope. Alkenylation with alkyl acrylates afforded the desired products **122a–c** in good yields, while only moderate yields were obtained when methyl vinyl ketone and acrylamide were used (**122d** and **122e**). Styrenes substituted with both EDGs and EWGs were well-tolerated, and the desired products **122f–k** could be prepared in 65–87% yields. Interestingly, vinyl acetate provided compound **122l** resulting from the loss of acetate in low yield (26% yield). Finally, C4-olefination of **121** with vinyl trimethylsilane and 1-phenyl-1,3-diene afforded **122m** and **122n** in 84% and 52% yield, respectively. Compound **121** was transformed into homophenylalanine derivative **123f** in good overall yield in a control experiment following hydrolysis with AcCl–MeOH and reduction of the double bond with palladium on carbon (Pd/C).

Interestingly, Glorius and co-workers reported a rhodium(III)-catalyzed oxidative olefination of vinylic C–H bonds.⁷⁴ Suitable reaction substrates encompassed acrylates, acrylamides, and acetamidoacrylates; however, enamides were unreactive. Using $[\text{RhCp}^*\text{Cl}_2]_2$ and AgSbF₆ together with Cu(OAc)₂ in *t*AmyLOH, acetamidoacrylates **124** were readily reacted with various terminal alkenes, thus giving access to $\alpha,\beta,\gamma,\delta$ -unsaturated amino acids in good yields and good 2Z-diastereoselectivities (Scheme S7). Notably, no homocoupling products were observed. The olefination of methyl 2-acetamidoacrylate and methyl 2-(2,2,2-trifluoroacetamido)acrylate with styrene afforded products **125a** and **125b**, respectively, as a separable mixture of 2Z- and 2E-diastereoisomers. The major isomers **2Z-125a** and **2Z-125b** were isolated in 75% and 50% yield, respectively. Notably, the desired product **2Z-125c**, prepared from the coupling of methyl 2-(N-methylacetamido)acrylate bearing a tertiary acetamide DG, with styrene was obtained in a decreased albeit still good 60% yield.

Styrenes bearing both electron-withdrawing and electron-donating substituents were also well-tolerated (2Z-**125d**–2Z-**125k**, 64–76% yields). Interestingly, no dehalogenation or Heck cross-coupling side-products were observed with styrenes bearing halide substituents such as chloride and bromide. Furthermore, sterically demanding styrenes bearing a methyl and chlorine substituents in an *ortho*-position, as well as 2-vinylnaphthalene, afforded the products 2Z-**125j**, 2Z-**125k**, and 2Z-**125l** in 71%, 75%, and 64% yield, respectively. Finally, the coupling products of methyl 2-acetamidoacrylate with *n*-butyl acrylate **125m**, phenyl vinyl sulfone **125n**, and *trans*-1-phenyl-1,3-butadiene **125o** were obtained as an inseparable mixture of diastereoisomers in 69%, 82%, and 64% yield, respectively. These compounds are interesting building blocks as they can be subjected to α,β -selective asymmetric dehydrogenation to afford valuable chiral amino acids.⁷⁵

6. CROSS-DEHYDROGENATIVE COUPLING VIA IONIC INTERMEDIATES

6.1. Background

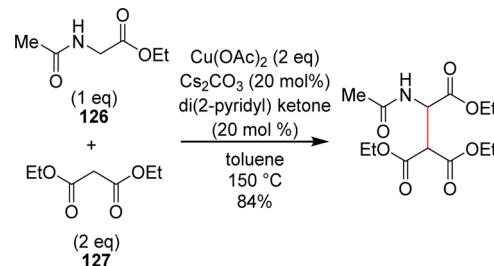
Reactions following a mechanism that involves ionic intermediates represent a major area of research in the CDC field.^{18a,c} Like in C–H functionalization via ionic intermediates (see section 4), the transition metals here do not react by forming M–C complexes but contribute to the polar C–C bond formation between an electrophilic (generated by metal-catalyzed C–H bond oxidation) and a nucleophilic (generated by deprotonation of acidic C–H bond) species. Interestingly, both transition metals and a combination of transition metals

with organocatalysts have been used to catalyze CDC reactions. In contrast with CDC reactions involving organometallic intermediates in which C(sp²)–H bonds were activated, in CDC reactions via ionic intermediates the C–C bond is formed between two C(sp³)–H bonds or between a C(sp³)–H and a C(sp)–H bond.^{18b} Among the substrates capable of undergoing oxidative activation are C–H bonds α to a tertiary nitrogen atom, tetrahydroisoquinolines, benzylic ethers, diphenylmethanes, and glycine derivatives. In addition to expanding the range of substrates, the development of enantioselective CDC reactions represents the most challenging task for organic chemists.

6.2. Cross-Dehydrogenative Coupling in Amino Acids and Peptides

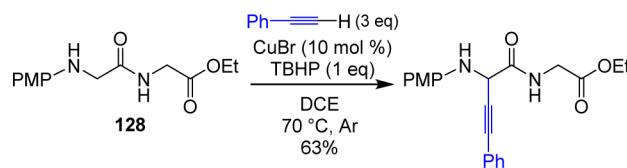
Among the pioneers in the field of CDC reactions, Li and co-workers were the first to apply the ionic CDC to glycine derivatives and peptides.⁷⁶ After an extensive screening, they identified the following optimized conditions for the coupling between the C(sp³)–H bond of *N*-acetyl ethyl ester protected glycine **126** (1 equiv) and the C(sp³)–H bond of ethyl malonate **127** (2 equiv): Cu(OAc)₂ (2 equiv), di(2-pyridyl)-ketone (20 mol %), and Cs₂CO₃ (20 mol %) in toluene at 150 °C (Scheme S8).⁷⁶

Scheme S8. CDC of Glycine Derivative **126** with Ethyl Malonate⁷⁶



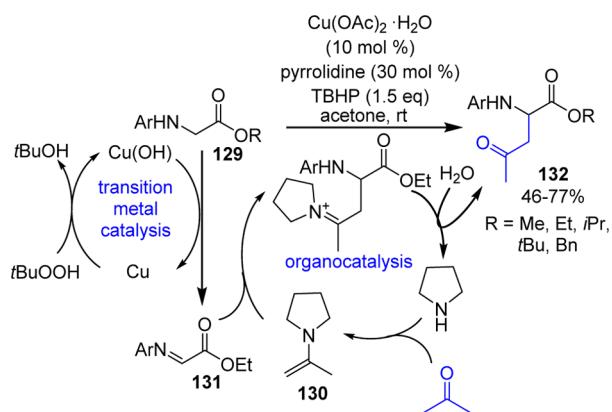
In the presence of a base, the stabilized carbanion generated from the malonate reacts in a Mannich-type reaction with the imino ester formed by copper-catalyzed oxidation of the glycine derivatives. Various glycine derivatives and malonates could be used under these reaction conditions. In addition to malonate, aromatic alkynes could be used as the nucleophilic species with N-PMP glycine amide substrates using CuBr as the catalyst and TBHP as the oxidant at room temperature. In this case, the terminal alkyne forms a copper acetylide, which undergoes nucleophilic addition to the imine intermediates. Interestingly, N-PMP glycine ester failed to provide the desired coupling products. The reaction was then attempted on the dipeptide *N*-PMP-Gly-Gly-OEt **128**, which as expected was specifically functionalized at the *N*-terminal glycine, as depicted in Scheme S9, when higher reaction temperatures were used.⁷⁶

Scheme S9. α -Functionalization of Dipeptide **128** via CDC with Phenylacetylene⁷⁶



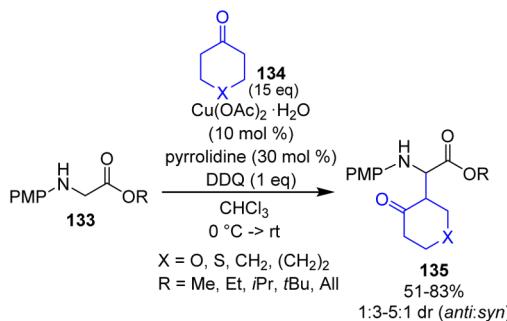
Building on Li's work,⁷⁶ Xie and Huang achieved the CDC of N-PMP glycine esters **129** with ketone by cooperative metal and organocatalysis.⁷⁷ Using TBHP (1.5 equiv) and both Cu(OAc)₂·H₂O (10 mol %) and pyrrolidine (30 mol %) as the catalysts at room temperature, Xie and Huang successfully coupled acetone with a wide range of *N*-aryl glycine esters in good yields. This dual catalytic effect results from the formation of an enamine (**130**) as the nucleophilic intermediate derived in situ from acetone and pyrrolidine, which reacts with the electrophile **131** generated from the copper-catalyzed oxidation of the glycine derivative **129** (Scheme 60).

Scheme 60. Cooperative Catalytic CDC Reaction with Acyclic Ketones⁷⁷



Although attempts to carry out the coupling of **133** with more hindered cyclohexanones **134** failed under these reaction conditions. Changing the oxidant to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded the coupling products **135** in good yields (Scheme 61).⁷⁷

Scheme 61. Cooperative Catalytic CDC Reaction with Cyclic Ketones⁷⁷



Interestingly, when a mixture of acetone and cyclohexanone was subjected to the reaction conditions in the presence of TBHP, only the coupling product from the acyclic ketone was isolated. On the other hand, in the presence of DDQ, only the coupling product from the cyclic ketone was formed. Similarly, Liu et al.⁷⁸ developed a cooperative CDC reaction between *N*-arylated glycine ester **133** and cyclic ketone **134** catalyzed by iron salts, DDQ, and pyrrolidine. Linear ketones **136** were found to be unreactive under these reaction conditions (Scheme 62), thus supporting Xie and Huang's previous findings.⁷⁷

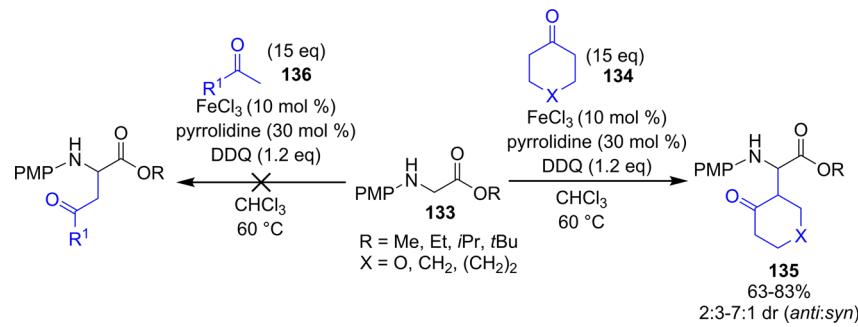
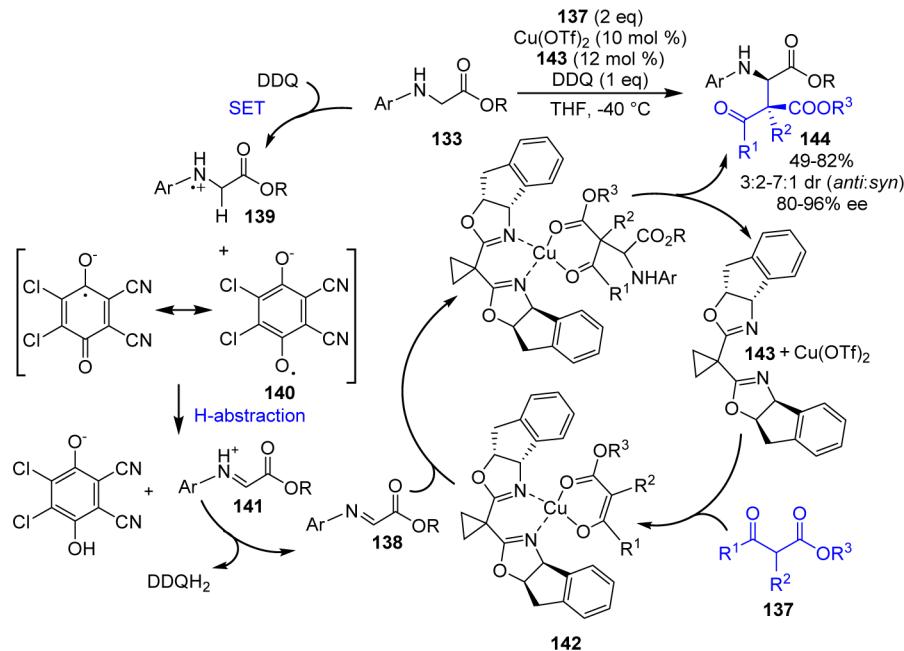
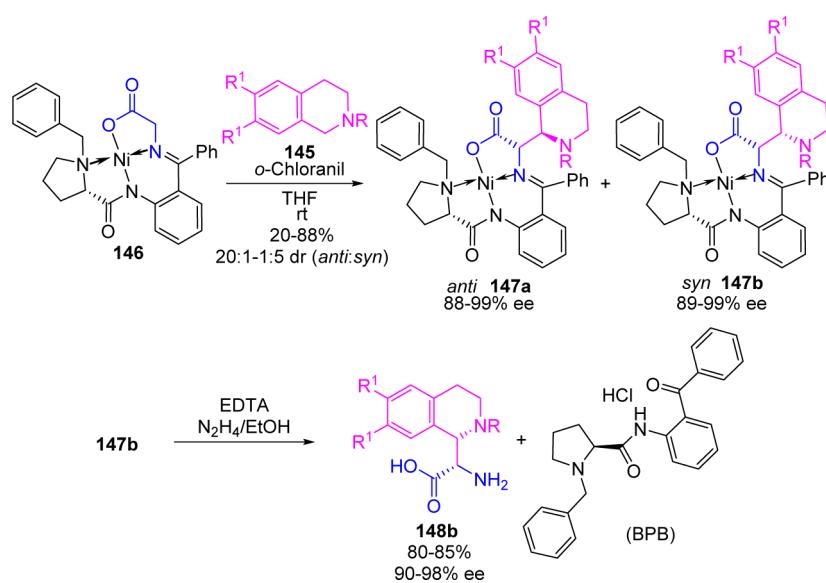
Furthermore, Liu et al.⁷⁸ illustrated the importance of the choice of solvent for the CDC reaction of glycine ester derivatives. While in CH₂Cl₂ no reaction occurred, replacing CH₂Cl₂ by DCE the coupling product was obtained, albeit in poor yield (10% yield). Finally, CHCl₃ was found to be the best solvent for the reaction, providing the desired product in 51% yield and up to 6:1 *anti:syn* ratio.

In efforts to develop an asymmetric version of the copper-catalyzed CDC reaction, Xie and Huang first investigated the effect of chiral ligands for the Cu(OAc)₂, but only racemic coupling products were obtained. However, using chiral pyrrolidines afforded up to 15% ee.⁷⁷ Although the enantiomeric excesses remained poor, this discovery paved the way for the development of catalytic asymmetric CDC reaction. Wang and co-workers focused on the stereoselective CDC reaction between *N*-arylated glycine esters **133** and β -ketoesters **137**.⁷⁹ After screening of various transition-metal catalysts, bisoxazoline (BOX) ligands, and solvents, the optimized reaction conditions summarized in Scheme 63 were identified, which afforded good yields, moderate diastereoselectivities, and high enantioselectivities.

Similar to the role of the Cu/TBHP, DDQ allows the oxidation of the glycine derivative to the imine **138**. First, DDQ accepts an electron through SET to form the radical cation **139** and the radical anion **140**. Next, the radical oxygen abstracts the α -hydrogen, thus yielding the iminium **141**, which after deprotonation releases DDQH₂ and the imine intermediate **138**. The latter undergoes nucleophilic attack by the chiral Lewis acid-bonded nucleophile **142**, itself derived from the chelation of β -ketoester **137** with the copper complex **143**, hence affording the desired coupling product **144** (Scheme 63).

Inspired by the work of Wang and co-workers,⁷⁹ who also extended their CDC reaction to the coupling of *N*-aryl tetrahydroisoquinoline with Horner–Wadsworth–Emmons (HWE) reagents, Zhou et al.⁸⁰ published the first asymmetric oxidative coupling of *N*-aryl tetrahydroisoquinoline **145** with a glycine equivalent. Whereas glycine derivatives are commonly used as the electrophile in CDC reactions, in this report, the chiral nickel(II) glycinate complex **146**, originally developed by Belokon et al.,⁸¹ was employed as the nucleophilic partner. *o*-Chloranil was identified as the best oxidant affording the desired coupling products **147** in good yield, good *syn:anti* ratio, and excellent diastereoselectivity. The chiral complex of glycine Schiff base **146** conferred an excellent *Si*-face selectivity at room temperature under the oxidative reaction conditions. Interestingly, while increasing the reaction temperature to 60 °C afforded a better yield, poorer diastereoselectivity was obtained; on the other hand, decreasing the temperature to 0 °C considerably decreased the yield. Attempts to carry out mild acidic hydrolysis failed to release the free amino acids; however, the complexes were successfully decomposed using a solution of N₂H₄·H₂O/EtOH with ethylenediaminetetraacetic acid (EDTA). The amino acids **148b** were obtained in good yields and good to excellent ee. Furthermore, the chiral (S)-2-[*N*-(*N'*-benzyl-prolyl)amino]benzophenone (BPB) ligand was recovered and recycled (Scheme 64).

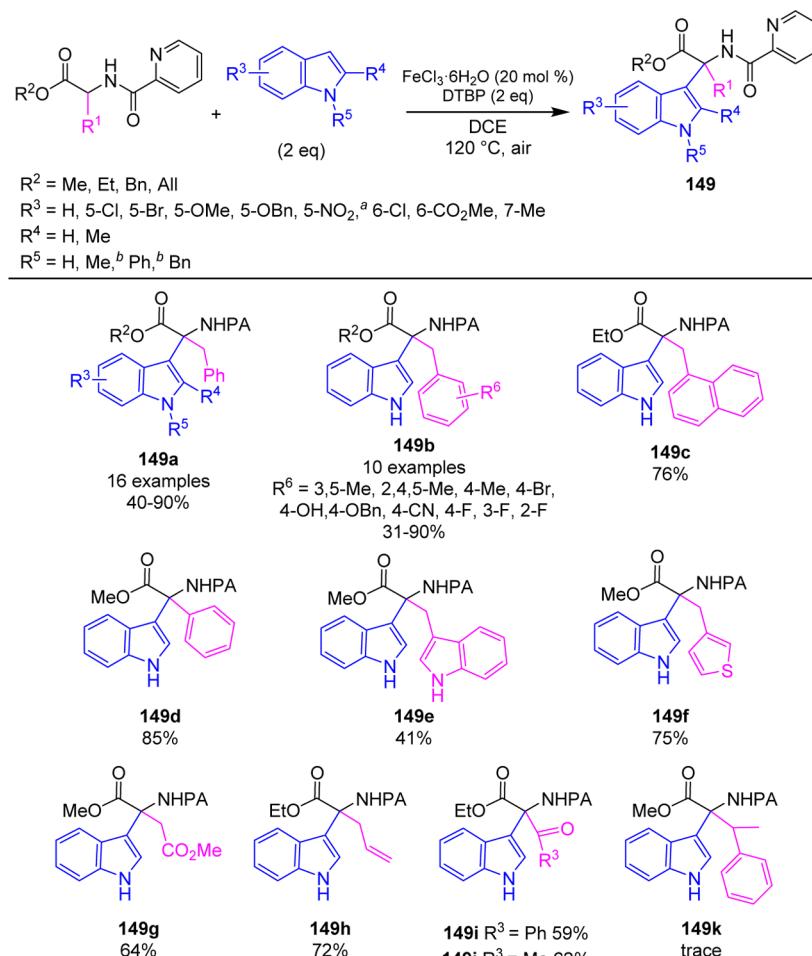
In an effort to extend the use of CDC reactions to the synthesis of α,α -disubstituted amino acids, You and co-workers proposed that the presence of a coordinative group at the *N*-terminus of the glycine derivative could facilitate the formation and subsequent reaction of the necessary ketimine intermediate.⁸² Among the various coordinating groups tested for the oxidative C(sp³)–H/C(sp³)–H coupling of phenylalanine

Scheme 62. Cooperative Catalytic CDC Reaction with Ketones Catalyzed by Iron and Pyrrolidine⁷⁸Scheme 63. Catalytic Asymmetric CDC of Glycine with β -Ketoesters⁷⁹Scheme 64. Enantioselective CDC Reaction between Tetrahydroisoquinoline and Chiral Ni(II) Glycinate⁸⁰

ester with indole, the PA-directing group gave the best result (90% yield). Furthermore, PA is ideal as it can be easily removed to afford the free amino acid. A wide range of

substituted indoles could be reacted with phenylalanine ester derivatives affording the coupling products 149a (16 examples) in good yields. The coupled products of substituted phenyl-

Scheme 65. Synthesis of Quaternary Amino Acids via Iron-Catalyzed CDC of Glycine Derivatives Bearing a PA-Coordinative Group with Indole Nucleophiles^{82a}



^a(a) 130 °C; (b) di-*tert*-butyl peroxide (DTBP) (1.5 equiv).

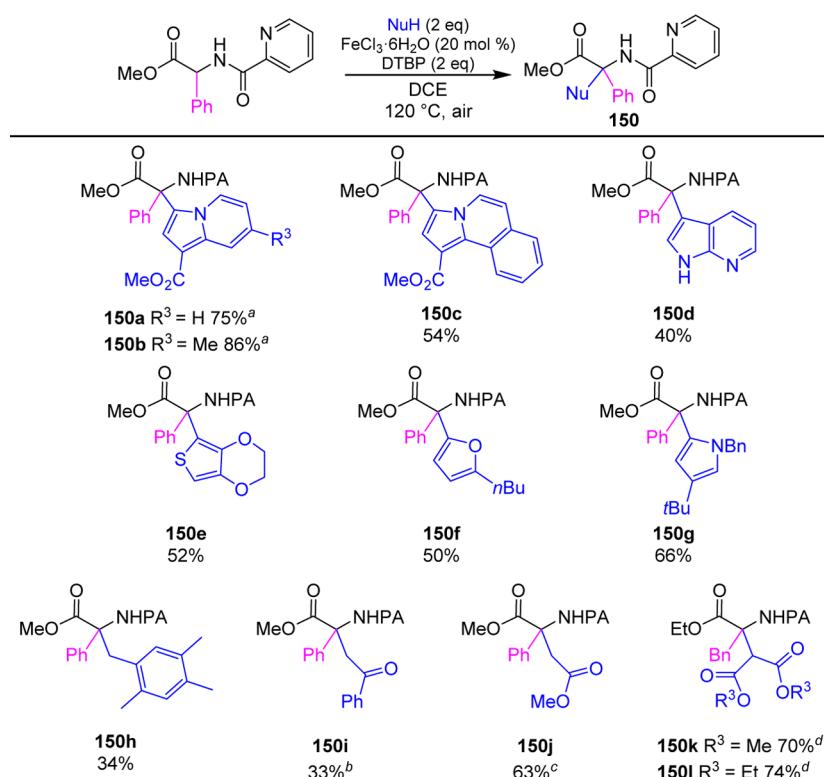
alanines **149b** (10 examples), 3-(1-naphthylalanine) **149c**, arylglycine **149d**, tryptophan **149e**, 3-(3-thienyl)alanine **149f**, aspartic acid methyl ester **149g**, allylglycine **149h**, and β -ketoamino acids **149i–j** were obtained in good yields. Unfortunately, the β,β -disubstituted alanine did not afford a good substrate for the reaction and afforded only a trace amount of the desired compound **149k**. You's synthesis of quaternary amino acids **149a–k** via CDC reaction using indole nucleophiles is represented in Scheme 65.

Not only did indoles react but also other types of electron-rich heteroaryls were found to be suitable nucleophiles. The coupling of phenylglycine with indolizines, azaindole, thiophene, furan, and pyrrole afforded the quaternary amino acids **150a–g** in moderate yields. Furthermore, the use of 1,2,3,4-tetramethylbenzene as well as trimethyl(1-phenylvinyloxy)silane as nucleophile was successful under these reaction conditions, affording compounds **150h** and **150i**, respectively. Interestingly, the coupling of dimethylmalonate with *N*-PA-phenylglycine ester yielded the product of the decarboxylation **150j**, while the coupling of *N*-PA-phenylalanine with dimethyl- and diethylmalonate afforded the desired products **105k** and **150l**, respectively (Scheme 66).

7. CONCLUSION AND OUTLOOK

With the emergence of peptides and peptidomimetics on the front stage of pharmaceutical research, the interest for novel methodologies for the rapid preparation of amino acids has been revived. Simultaneously, the efforts of organic chemists in the exciting field that is C–H functionalization chemistry have led to considerable progress. Recent advances in all types of C–H functionalization reactions have been employed to generate efficient ways to synthesize the precious building blocks and even directly derivatize peptides. C–H functionalization of $\text{C}(\text{sp}^2)$ –H bonds via organometallic intermediates has been well-studied and provides a practical technique for the borylation, halogenation, acetoxylation, and arylation of aromatic amino acids; protocols for 1° and 2° $\text{C}(\text{sp}^3)$ –H functionalization are also slowly arising. Notably the use of bidentate directing groups has allowed the β - and γ -arylation of various amino acids. Moreover, the C–H functionalization via organometallic intermediates strategy has also been employed for the site-specific functionalization and the macrocyclization of peptides. C–H functionalization via carbenoid and ionic intermediates are less developed but represent complementary approaches. The former that allows the functionalization of $\text{C}(\text{sp}^3)$ –H bonds has been applied to the preparation of β_2 -amino acids. The latter permits the synthesis of racemic

Scheme 66. Synthesis of Quaternary Amino Acids via Iron-Catalyzed CDC of Glycine Derivatives Bearing a PA-Coordinative Group with Other Nucleophiles^{82a}



^a(a) $\text{Cu}(\text{OAc})_2$ (20 mol %), dioxane, 110 °C; (b) NuH (4 equiv); (c) NuH (3 equiv), DTBP (3 equiv); (d) phenylalanine ethyl ester derivatized with the PA-DG was used as the electrophilic partner.

arylglycines by side-chain insertion into the α -C(sp³)–H bond of a glycine derivative.

Finally, the more difficult cross-coupling dehydrogenative reaction via organometallic intermediate formation has also been achieved, but only a few examples of the Heck-type reaction for the functionalization and synthesis of α -amino acids through introduction of the side-chain have been reported. Nevertheless, this type of CDC reaction is appropriately complemented by the CDC via ionic intermediates, which allows the C–C bond formation through C(sp³)–H functionalization and has proved more fruitful in regards to its application to the synthesis of amino acids. The use of tandem transition metal/organocatalysis has been developed to expand the otherwise narrow substrate scope of ionic CDC reactions. Recently, thanks to the use of coordinating group-assisted CDC, quaternary amino acids that are difficult to access through traditional methods were readily prepared. Furthermore, both chiral auxiliary and chiral ligands have been employed to extend the reaction to an asymmetric version.

Although C–H functionalization represents a timely approach, which answers the needs for greener and more efficient chemistry, many challenges remain. First, the low reactivity of the C–H bond is still an important limitation as outlined by the lack of a general method for the organometallic C(sp³)–H alkylation. The regioselectivity of the reaction is another restriction that will need to be addressed. Indeed, the regioselective non-directed C–H functionalization is to date only applicable to very few substrates, and the scope of existing directing groups is considerably narrow. Furthermore, similar substrate scope limitations exist for the ionic type reaction.

These constraints in terms of regioselectivity hamper the development of efficient methods for the late-stage functionalization of complex peptides. Such methodology would however be highly desirable for the increasingly important proteomics and peptide-based drug discovery as it would effect the rapid derivatization of a lead peptide into a large array of peptidomimetics. Another difficulty lies in the mandatory use of high catalyst loadings and sacrificial oxidants, which counterbalanced the “green” image of C–H functionalization reactions. Finally, in the days of asymmetric synthesis, the rare examples of asymmetric C–H functionalization reactions clearly indicate that significant progress is needed in that area.

However, thanks to the increase of mechanistic studies, chemists continually develop a better understanding of the mechanical aspects ruling these reactions and should in the near future overcome these issues. Attention is now turning toward the design of novel ligands, which should address many of the remaining challenges, as they did for traditional cross-coupling reactions. They should notably participate in expanding the substrate scope by increasing the reactivity and regioselectivity of the C–H activation step. The use of chiral ligands has already led to a few examples of asymmetric synthesis; however, it is hoped that with continued efforts in that area, a general asymmetric C–H functionalization protocol will soon be available. By increasing the turnover numbers, ligands should also eventually allow the use of ultralow catalyst loadings. This advancement together with the use of molecular oxygen as sole oxidant would promote C–H functionalization as a safer, atom-economical, and more environmentally friendly process capable of outcompeting traditional cross-coupling in terms of cost and practicality. Although the future of C–H functionalization

seems bright, it is only once these goals are achieved that C–H functionalization will become the method of choice for both the laboratory and the industrial scale synthesis of amino acids and peptides.

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Notes

The authors declare no competing financial interest.

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Anaïs F. M. Noisier obtained her engineer's degree in 2009 from the Ecole Nationale Supérieure de Chimie de Clermont-Ferrand (ENSCCF), France. She then joined the research group of Distinguished Professor Margaret A. Brimble at the University of Auckland (New Zealand), where she worked on the preparation of a peptidomimetics library using organometallic chemistry and later on the development of a new methodology for the asymmetric synthesis of unnatural amino acids (U.S. patent application no. 61/729,810; 26/11/2012) in collaboration with Dr. Craig S. Harris at AstraZeneca Research Centre (Reims, France). She received her doctorate in 2013 and was awarded the Dean of Graduate Studies List as well as the L. H. Briggs Memorial Prize for best Ph.D. thesis within the School of Chemical Sciences. Anaïs is currently a Marie Curie postdoctoral researcher in the group of Fernando Albericio at the Institute for Research in Biomedicine of Barcelona (Spain).



Margaret Brimble is a Distinguished Professor and Director of Medicinal Chemistry at the University of Auckland, New Zealand. Her research program focuses on the synthesis of bioactive natural products and the synthesis of peptides/peptidomimetics. She won the 2010 Royal Society of Chemistry Natural Products Award, and was named the 2007 L'Oréal-UNESCO Women in Science laureate in

Materials Science for Asia-Pacific. In 2012 she was awarded the RSNZ Rutherford Medal (New Zealand's top science prize) and conferred the Queen's Honour *Companion of the New Zealand Order of Merit*. She has published over 350 papers, 25 patents, and is vice-President of IUPAC Organic and Biomolecular Chemistry Division III. She also developed the peptidomimetic NNZ2566, which is phase 2b human clinical trial for Traumatic Brain Injury and has been granted orphan drug status for Fragile X Syndrome by the FDA.

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ABBREVIATIONS

Ac	acetyl
Ad	adamantly
Ala	alanine
All	allyl
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOX	bis(oxazoline)
BPB	(S)-2-[N-(N'-benzyl-prolyl)amino]benzophenone
BPin	pinacol boronate
BQ	<i>p</i> -benzoquinone
Bz	benzoyl
Cbz	carboxybenzyl
CDC	cross-dehydrogenative coupling
CMD	concerted metallation-deprotonation
COD	1,5-cyclooctadiene
conv	conversion
Cp	cyclopentadiene
Cp*	1,2,3,4,5-pentamethyl cyclopentadiene
Cy	cyclohexyl
DavePhos	2-dicyclohexylphosphino-2'-(<i>N,N'</i> -dimethylamino)-biphenyl
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Δ	reflux
DG	directing group
DMA	<i>N,N</i> -dimethylacetamide
DMF	<i>N,N</i> -dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
DMSO	dimethyl sulfoxide
dr	diastereoisomeric ratio
DTBP	di- <i>tert</i> -butyl peroxide
dtbipy	4,4'-di- <i>tert</i> -butyl-2,2'-bipyridine
EDG	electron-donating group
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
eq	equivalent
Et	ethyl
EWG	electron-withdrawing group
FDA	food and drug administration
Fmoc	fluorenylmethyloxycarbonyl
Gly	glycine
Het	hetero
HFIP	hexafluoroisopropanol
His	histidine
HPLC	high-performance liquid chromatography

HWE	Horner–Wadsworth–Emmons
iPr	isopropyl
Leu	leucine
LG	leaving group
Ln	L-type ligand
Lys	lysine
m	meta
M	metal or molar
Me	methyl
MIA	2-methoxyiminoacetyl
MTBE	methyl <i>tert</i> -butyl ether
MW	microwave
nBu	<i>n</i> -butyl
ND	not determined
nPr	<i>n</i> -propyl
Nu	nucleophile
o	ortho
p	para
PA	picolinoyl
Pd/C	palladium on carbon
PG	protecting group
Ph	phenyl
Phe	phenylalanine
Phth	phthaloyl
PIP	2-(pyridine-2-yl)isopropyl
Piv	pivaloyl
PMP	<i>para</i> -methoxyphenyl
QPhos	1,2,3,4,5-pentaphenyl-1'-(di- <i>tert</i> -butylphosphino)-ferrocene
rt	room temperature
SET	single-electron transfer
S _N 2	nucleophilic substitution of order 2
SPPS	solid-phase peptide synthesis
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
tBu	<i>tert</i> -butyl
Teoc	2-(trimethylsilyl)ethoxycarbonyl
Tf	trifluoromethanesulfonyl
Tfa	trifluoroacetyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Tol	tolyl
Trp	tryptophan
Tyr	tyrosine
Val	valine

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