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Letter

C−C Cross-Coupling of *N*-Terminal Glycine Dipeptides Enabled by a Cationic Pd-Phosphine Catalyst

Igor Beckers,* Giovanna Mejia, Pernilla Korsgren, Dirk De Vos, and Magnus J. Johansson*

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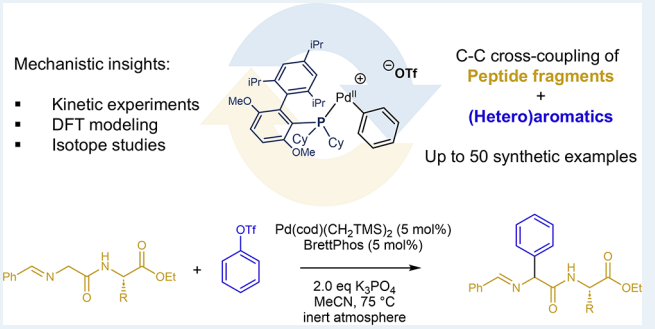
ABSTRACT: Pd-catalyzed cross-coupling reactions are of key importance in the synthesis of C−C (linking, e.g., (hetero)aryls, alkenes, alkynes) and C−heteroatom bonds in the preparation of drug candidates. One such class of drug candidates encompasses peptides and peptidomimetics, where peptide-like motifs contribute to their biological activity. Despite its importance, direct C−C cross-coupling on the peptide backbone remains elusive. In this work, we demonstrate the utility of cationic Pd-phosphine complexes for C(sp^3)−C(sp^2) (hetero)arylation of protected *N*-terminal glycine dipeptide fragments. The underlying catalytic mechanism was elucidated via kinetic experiments, computational modeling and isotope studies, and the synthesis of up to 50 medicinally relevant dipeptide carbon scaffolds was demonstrated.



KEYWORDS: *Pd-catalyzed cross-coupling, C−H functionalization, C(sp^3) cross-coupling, Homogeneous catalysis, Catalytic mechanisms*

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INTRODUCTION

Pd-catalyzed cross-coupling has become indispensable as a synthetic tool for medicinal chemists in the search for drug candidates.[1−7] In addition to the catalytic formation of bi(hetero)aryl C−C bonds with (hetero)aromatic drug scaffolds and wide range of possible C−heteroatom couplings,[8−14] it offers a highly practical approach to form C−C linkages with C(sp^2) in alkenylations and C(sp) in alkynylations.[15,16] Recent advances in cross-electrophile coupling target the linkage of C(sp^3) alkyl fragments to obtain more three-dimensional carbon scaffolds.[17−19] Alternatively, the α-arylation of esters, ketones and aldehydes affords a synthetic method for the formation of C(sp^3)−C(sp^2) bonds in α-position of a carbonyl via the corresponding enolates,[20] which was also extended to the arylation of glycine esters via the corresponding imine or tertiary amides with strong bases or Reformatsky reagents (Figure 1).[21−23] In spite of the importance of peptides in medicinal chemistry and biology at large, such catalytic cross-coupling with the carbon backbone of peptide fragments remains elusive to date. We envisaged that the development of a catalytic system for such α-arylations of peptide bonds could open a direct route to construct phenylglycine derivatives in dipeptide fragments, which are pharmaceutically important motifs encountered in, e.g., antibiotics, peptidomimetics and recent drug approvals.[24−31]

In this work, we report on the Pd-catalyzed C−C cross-coupling of (hetero)aromatic (pseudo)halides and the *N*-terminal glycine in dipeptide fragments. Using a mechanism-guided approach, aided by kinetic profiling, computational modeling and *in situ* NMR analysis of isotope-enriched amino acid reactants, it was discovered that cationic Pd-phosphine complexes extend the C−C cross-coupling methodology to small peptide fragments. The catalyst effectively traps the enolate intermediate formed upon mild deprotonation of the *N*-terminal glycine and forms the desired C−C bond via a rate-limiting reductive elimination step. The scope of the catalytic cross-coupling was extensively studied in up to 50 synthetic examples, featuring functional group tolerance toward diversified (hetero)aromatic and peptide scaffolds with pharmaceutically relevant functionalities. This catalytic pathway for the cross-coupling of *N*-terminal glycine residues further extends the vast utility of Pd-catalyzed cross-coupling reactions toward the broader field of peptide chemistry.

RESULTS AND DISCUSSION

Catalyst Optimization and Kinetic Studies

In the pursuit of a catalytic system that could enable the C−C cross-coupling of (hetero)aromatic (pseudo)halides and peptide fragments, our optimization started with the α-arylation of individual glycine esters as literature benchmark

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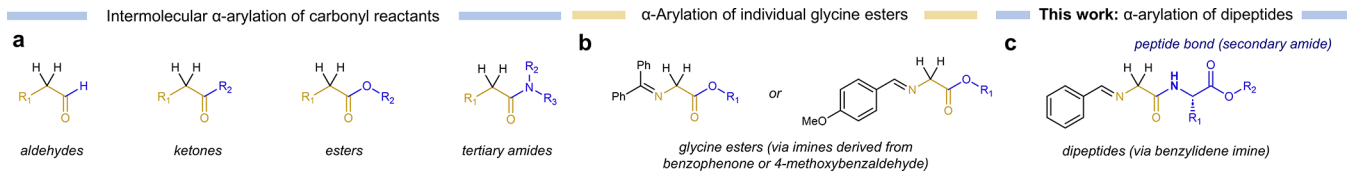

Figure 1. a) Overview of common carbonyl reactants used in previous α-arylation reactions.[20] Tertiary amides can be used with strong bases or Reformatsky reagents.[22,23] b) α-Arylation of imines derived from individual glycine esters using a mild base by Hartwig and co-workers.[21] Benzophenone or electron-donating 4-methoxybenzaldehyde was used to avoid side-reactivity. c) This work enables the α-arylation of dipeptides enabled by a cationic Pd-phosphine catalyst. Secondary amides (i.e., peptide bonds) are well tolerated via the trapping of enolate intermediates.

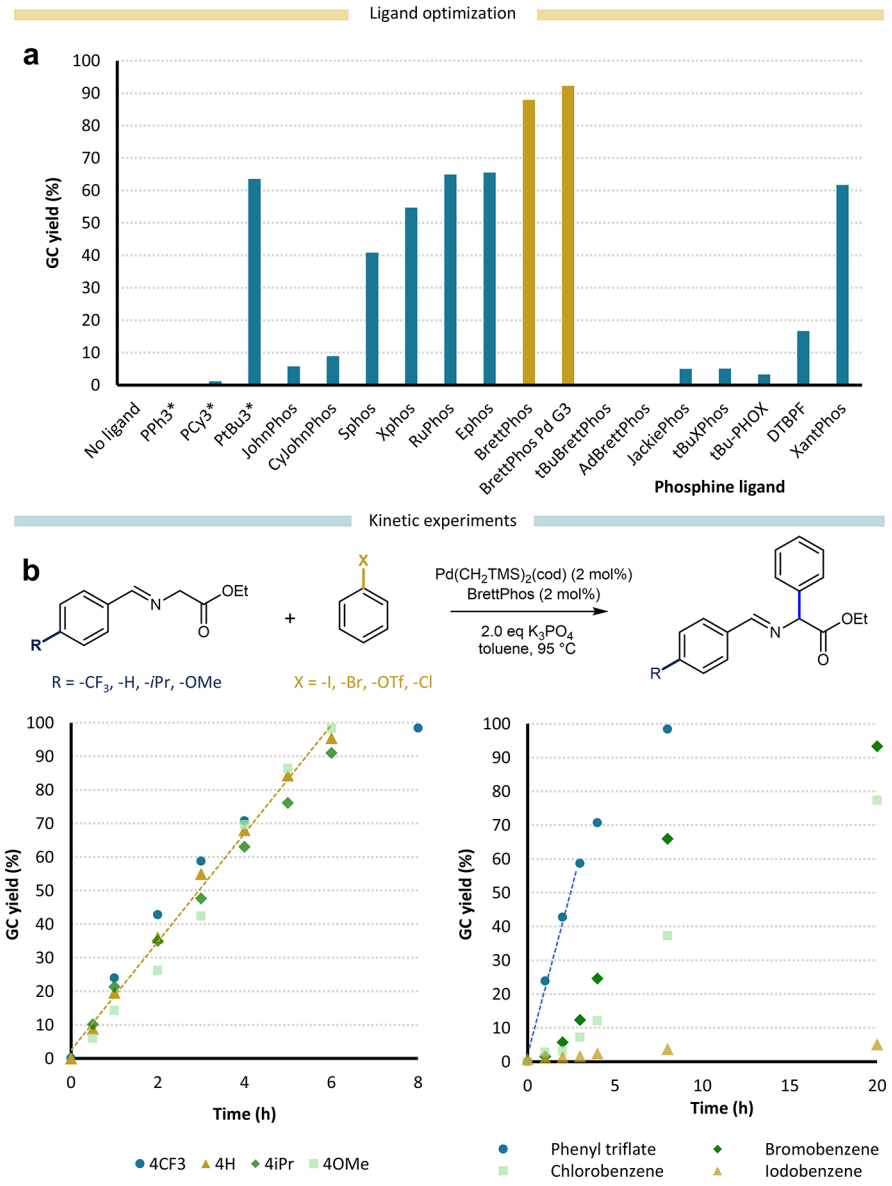

Figure 2. a) Catalyst optimization and b) kinetic studies. Reaction conditions: Pd(cod)$(CH_2TMS)_2$ (2 mol%), phosphine ligand (2 mol%), 4-substituted benzylidene imine Gly-OEt (1.0 equiv), phenyl (pseudo)halide (1.0 equiv), anhydrous K_3PO_4 (2.0 equiv), anhydrous toluene (0.05 M), 95 °C, 0−20 h, Ar atmosphere. *Phosphine ligand added as 4 mol% of the corresponding tetrafluoroborate salt.

conditions.[21] A ligand screening was performed, ranging from simple monophosphine ligands to dialkyl biaryl phosphines with varying substitution patterns and bidentate phosphine ligands (Figure 2a, Table S1, Figure S1). Interestingly, our experiments revealed that dicyclohexyl biaryl monophosphine ligands, in particular BrettPhos, were highly effective ligands for this C−C cross-coupling reaction. A sharp yield decline was found with more sterically hindered variants, e.g., bearing *tert*-butyl and adamantyl substituents. An in-depth kinetic profiling of the reaction was performed to investigate the effects of electronic substituents on the substrate and the leaving group on the phenyl (pseudo)halide coupling partner (Figure 2b, Tables S2−S6, Figures S2 and S3). Variation of the substituent on *para*-position of the benzylidene imine of the glycine

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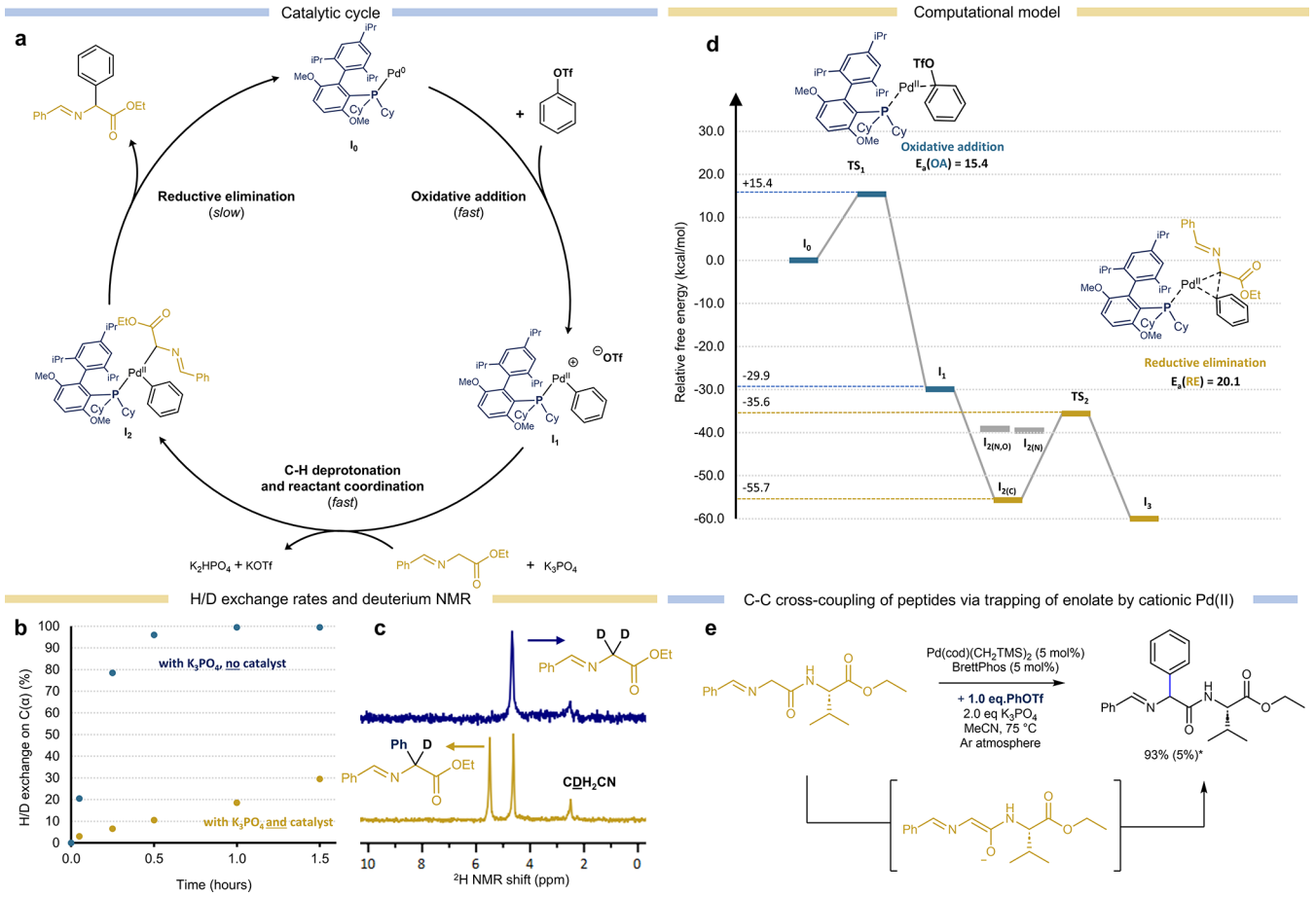

Figure 3. Mechanistic investigation of the catalytic cycle. a) Schematic of the underlying catalytic cycle and the elementary steps. b) Study of H/D exchange rate via ^{1}H qNMR in CD_3CN under optimized conditions or in the absence of catalyst. c) Qualitative ^{2}H NMR spectra obtained after H/D exchange reactions. d) Free-energy diagram of the catalytic reaction calculated via DFT (B3LYP-D3/Def2TZVP). $I_{2(N,O)}$, $I_{2(N)}$ and $I_{2(C)}$ represent different binding modes of the enolate to Pd via *N,O*- (−38.3 kcal/mol), *N*- (−39.5 kcal/mol) and *C*-coordination (−55.7 kcal/mol) respectively (see computational details in the Supporting Information). e) Cross-coupling of the Gly-Val-OEt dipeptide fragment via trapping of the enolate intermediate by a cationic Pd(II)-phosphine catalyst. Yield percentages given as ^{1}H qNMR yields. Reaction conditions: Pd(cod)$(CH_2TMS)_2$ (5 mol%), BrettPhos (5 mol%), Gly-Val-OEt benzylidene imine (0.05 mmol, 1.0 equiv), (hetero)aryl triflate (1.0 equiv), anhydrous K_3PO_4 (2.0 equiv), anhydrous MeCN (0.05 M), 75 °C, 24 h. *Reaction performed under benchmark reaction conditions for α-arylation (Table S7).

reactant with electron-withdrawing ($-CF_3$) or electron-donating (-*i*Pr, -OMe) groups showed that electronic effects no longer influence the outcome of the catalytic reaction, circumventing the selectivity issues in the arylation of such enolates reported in earlier work.[21] In addition to the successful coupling of phenyl chloride and bromide, we found that the reaction is in fact strongly accelerated by the choice of an aryl triflate as the electrophilic coupling partner. In the latter case, a clear (pseudo) zero order kinetics was observed. Solvent screening revealed a slight decrease in activity with MeCN as a polar aprotic solvent, but this activity might find use for polar peptides with drug-like properties (Table S2). In order to benchmark our conditions to previous α-arylation on individual glycine esters reported in literature,[21] four *N*-terminal glycine derivatives were tested in both conditions, revealing significantly improved ^{1}H qNMR yields in all cases (Table S7, Figures S4−S11).

Mechanistic Study Reveals That Cationic Pd Complexes Effectively Trap Enolate Intermediates

The reaction development was guided by new insights in the underlying catalytic mechanism (Figure 3a). The unusual reactivity order of PhOTf > PhBr > PhCl ≫ PhI in Pd-catalyzed cross-coupling contradicts a general rate-determining oxidative addition step and hints toward the importance of the weakly coordinating $^{-}$OTf anion in the overall catalytic cycle. The use of aryl triflates as the electrophilic coupling partner accesses cationic pathways in other cross-couplings, with the cationic Heck mechanism as a prominent example.[32−40] The formation of cationic Pd(II) after the oxidative addition promotes the coordination of the glycine imine derivative, whereas the requirement of halide abstraction could hamper cross-coupling in the case of PhBr. Rapid H/D exchange of the enolizable proton in C(α) position of the glycine reactant was observed via ^{1}H and ^{2}H NMR, mediated by K_3PO_4 in CD_3CN (Figure 3b and c, Table S8, Figures S12 and S13), in the absence of Pd catalyst. The presence of active catalyst drastically decreases the rate of H/D exchange, suggesting that the enolate intermediate is effectively trapped by the cationic Pd(II) complex. In addition, our *in situ* NMR studies of the ^{13}C-enriched amino acid reactant shows its degradation when stronger bases are used to form the enolate, and formation of $^{-}$OTf from PhOTf was observed via ^{19}F NMR using the stoichiometric Pd complex in MeCN-d_3 (Figures S15

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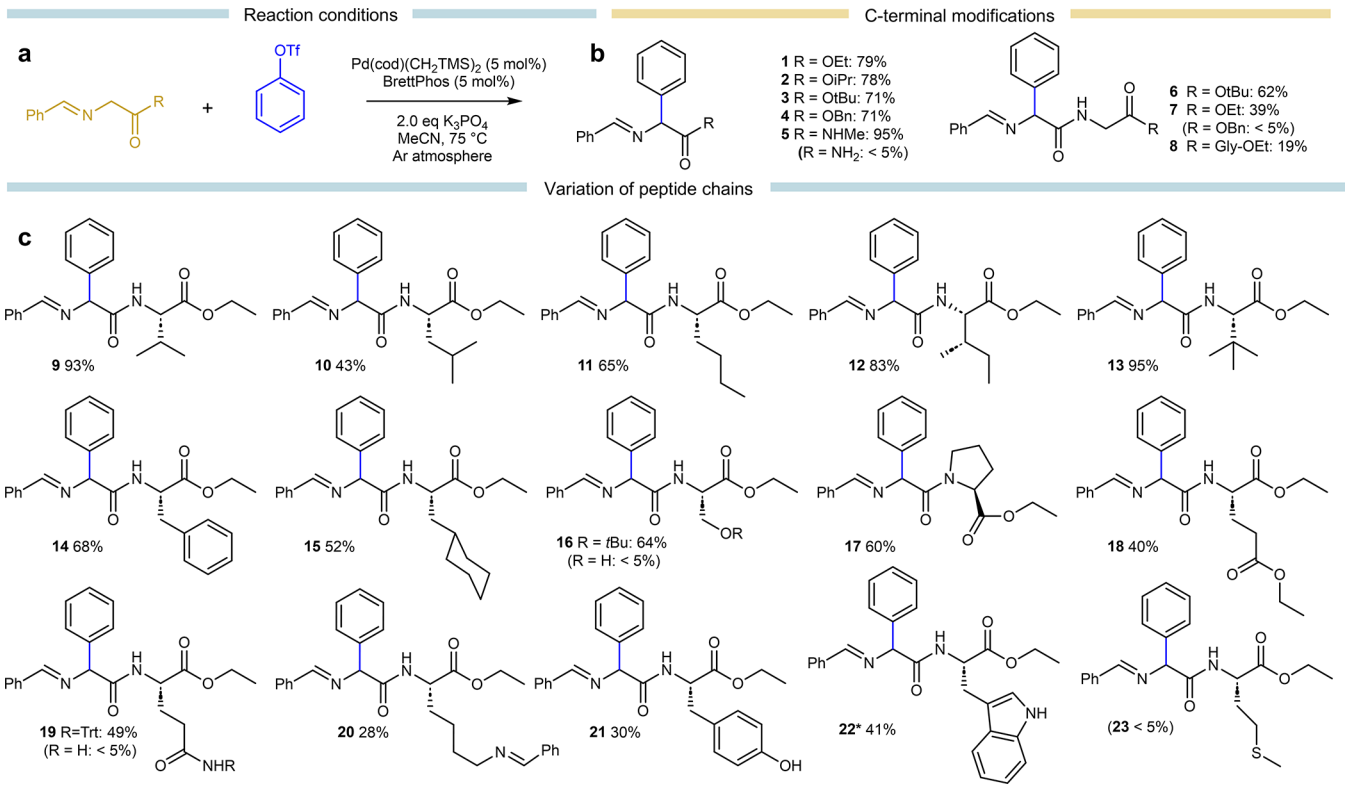

Figure 4. Scope of the Pd-catalyzed cross-coupling for the phenylation of various peptide fragments. Optimized reaction conditions (a) and corresponding substrate scope featuring various C-terminal modifications (b) and the variation of short peptide chains with N-terminal glycine residues (c). Reaction conditions: Pd(cod)(CH_2TMS)$_2$ (5 mol%), BrettPhos (5 mol%), peptide imine derivative (0.05 mmol, 1.0 equiv), (hetero)aryl triflate (1.0 equiv), anhydrous K_3PO_4 (2.0 equiv), anhydrous MeCN (0.01−0.05 M), 75 °C, 24 h. *For compound **22**, XPhos was used as the ligand.

and S16). This leaves the final reductive elimination as the rate-determining step, which is further supported by the observed zero order kinetics and the role of the dialkylbiaryl phosphine ligands to facilitate this catalytic step.[41] Our computational model aligns with this mechanistic view with calculated energy barriers of 15.4 and 20.1 kcal/mol for the oxidative addition and reductive elimination step respectively, showing that the latter step is disfavored by approximately 5 kcal/mol (Figure 3d).[42−45] These mechanistic insights highlight that the cationic Pd(II)-phosphine complex formed after oxidative addition rapidly traps the enolate formed on the *N*-terminal residue of a model peptide fragment (Figure 3e), enabling its α-arylation in excellent ^{1}H qNMR yield.

Extending the Scope of C−C Cross-Coupling to the α-Arylation of Dipeptide Chains

With the optimized catalytic conditions in hand (Figure 4a), we evaluated the scope of the reaction by gradually increasing the complexity of the dipeptide chains and (hetero)aromatic coupling partners. Alteration of the C-terminal functionality shows that secondary amides and dipeptides (**1**−**7**) are successfully cross-coupled on the N-terminal glycine residue (Figure 4b), whereas the arylation of triglycine ethyl ester as a tripeptide example (**8**) is limited by its poor solubility. The cross-coupling reaction was performed in good yields for a wide range of dipeptides bearing either natural or unnatural amino acid residues, including flexible aliphatic fragments such as Val, Leu, Nle and Ile (**9**−**12**) (Figure 4c).

The reaction remains largely unaffected by bulky side-chains on the neighboring amino acid residue, e.g., *t*-Leu, Phe, Cha and Ser(O*t*Bu) (**13**−**16**). The vicinity of a rigid Pro-residue is also well tolerated by the catalyst (**17**). The conventional side-chain protecting groups used in peptide synthesis counteract the otherwise inhibitory effect of metal-chelating motifs, further extending the scope toward hydrophilic amino acid residues such as Glu, Gln and Lys (**18**−**20**). The Gly-Tyr dipeptide fragment was cross-coupled in moderate yield as well (**21**). While Gly-Trp can be arylated under adapted catalytic conditions, the vicinity of a Met residue is a limitation of the synthetic method (**22**, **23**). Likewise, a diverse collection of (hetero)aromatic scaffolds were introduced on the *N*-terminal glycine residue ranging from apolar to polar functionalities with differences in steric hindrance and potential to coordinate transition metals (Figure 5). Phenyl triflates bearing a wide range of electron-donating and withdrawing groups as *para*-substituents are coupled in good yields (**24**−**30**), including the -Cl functional handle for further cross-coupling via Pd catalysis. Likewise, *meta*-substituted phenyl triflates are well tolerated in the reaction (**31**, **32**). Hydrophobic side chains on the phenyl ring can be cross-coupled, even the bulky adamantyl substituent (**33**−**36**). Pharmaceutically relevant, polar functionalities such as protected anilines, amides and ureas can also be accessed (**37**−**40**). Although generally challenging in Pd catalysis, thioether and sulfoxide functionalities are tolerated on a remote position to avoid metal-chelation (**41**, **42**). A sulfonamide derivative was cross-coupled as well, but in lower yield (**43**). Of particular importance in medicinal chemistry, a range of heteroaromatics are coupled in moderate yields, including quinoline, thiophene, pyrimidine and pyridines (**44**−**48**). Interestingly, the metal-chelating 2-phenylpyridine motif

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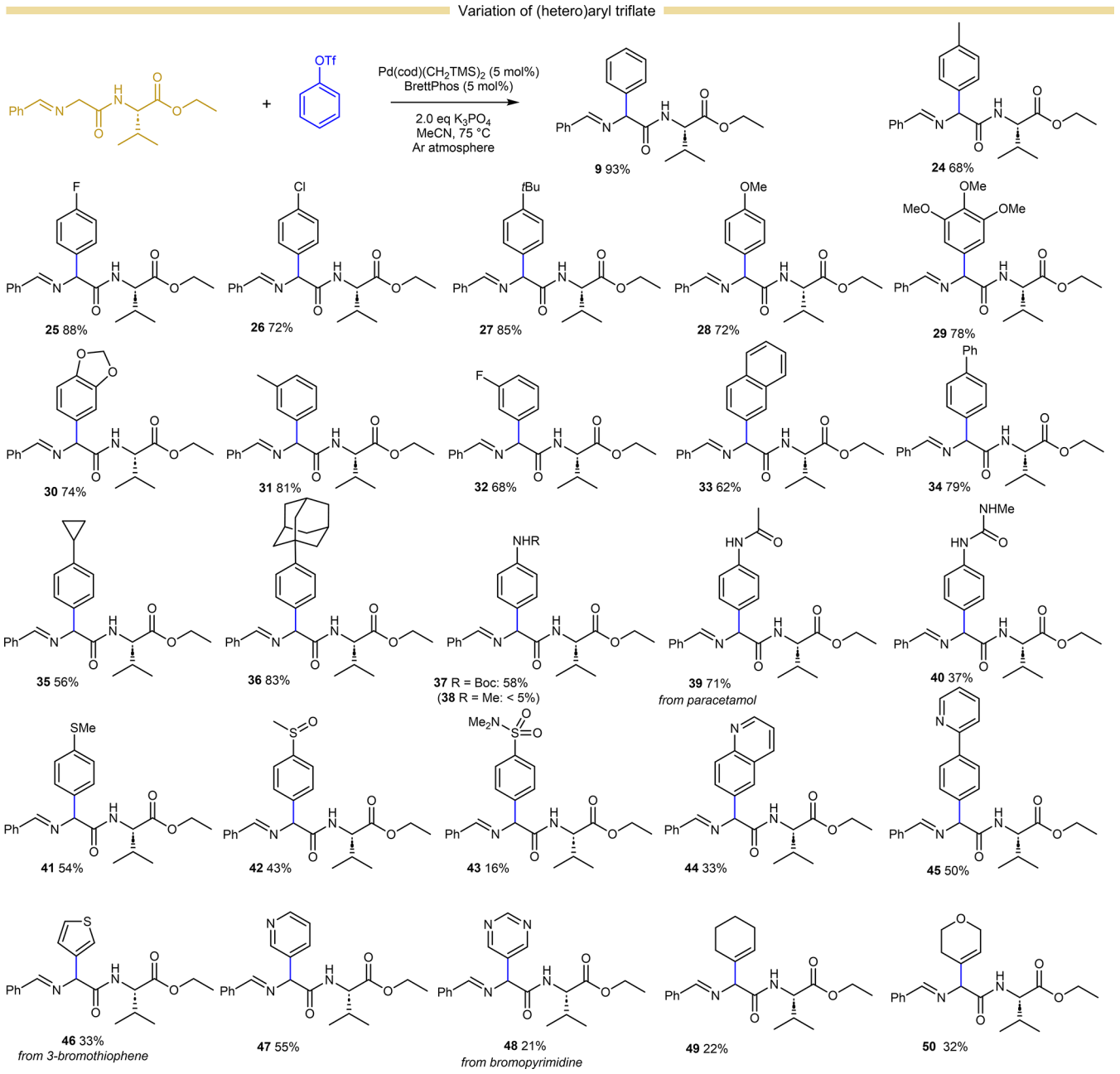

Figure 5. Scope of the Pd-catalyzed cross-coupling between a peptide fragment and a wide range of pharmaceutically relevant (hetero)aromatics. Reaction conditions: Pd(cod)(CH_2TMS)$_2$ (5 mol%), BrettPhos (5 mol%), peptide imine derivative (0.05 mmol, 1.0 equiv), (hetero)aryl triflate (1.0 equiv), anhydrous K_3PO_4 (2.0 equiv), anhydrous MeCN (0.01−0.05 M), 75 °C, 24 h.

(**45**) is tolerated by the Pd-phosphine catalyst. Finally, the cross-coupling also works on alkenyl triflates as nonaromatic coupling partners, giving access to dipeptide-linked alkenes for further diversification (**49**, **50**).[46−48]

CONCLUSION

To conclude, this research addressed the development of an effective catalytic system for C−C cross-couplings of *N*-terminal glycine residues in peptide fragments. The underlying catalytic cycle for α-arylation was studied, revealing a cationic Pd(II)-Phosphine that effectively traps the enolate formed on the *N*-terminal glycine residue of dipeptide chains. The cross-coupling reaction was demonstrated in the synthesis of a wide range of dipeptide scaffolds. We are convinced that this catalytic reaction will become an important synthetic tool in drug discovery to bridge the modalities of (hetero)aromatic molecules and peptide fragments.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.5c08711.

Experimental Section, supporting figures and tables, Cartesian coordinates of DFT calculations, chemical details and NMR characterization data (PDF)

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AUTHOR INFORMATION

Corresponding Authors

Igor Beckers − *Medicinal Chemistry, Cardiovascular, Renal and Metabolism (CVRM), Discovery Sciences, BioPharmaceuticals R&D, AstraZeneca, 431 83 Mölndal, Sweden; Centre for Membranes, Adsorption, Catalysis and Spectroscopy (cMACS), Department of Microbial and Molecular Systems, KU Leuven, 3001 Leuven, Belgium;* orcid.org/0000-0002-4363-4893; Email: igor.beckers@kuleuven.be

Magnus J. Johansson − *Medicinal Chemistry, Cardiovascular, Renal and Metabolism (CVRM), Discovery Sciences, BioPharmaceuticals R&D, AstraZeneca, 431 83 Mölndal, Sweden;* orcid.org/0000-0002-0904-2835; Email: magnus.j.johansson2@astrazeneca.com

Authors

Giovanna Mejia − *Compound Synthesis and Management, Discovery Sciences, BioPharmaceuticals R&D, AstraZeneca, 431 83 Mölndal, Sweden*

Pernilla Korsgren − *Compound Synthesis and Management, Discovery Sciences, BioPharmaceuticals R&D, AstraZeneca, 431 83 Mölndal, Sweden*

Dirk De Vos − *Centre for Membranes, Adsorption, Catalysis and Spectroscopy (cMACS), Department of Microbial and Molecular Systems, KU Leuven, 3001 Leuven, Belgium;* orcid.org/0000-0003-0490-9652

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.5c08711

Author Contributions

IB contributed to the conceptualization, methodology, investigation, funding acquisition, project administration and writing of the original draft of the manuscript. GM and PK contributed to the investigation. DDV and MJJ contributed to supervision and project administration. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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