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Letter

Modular Synthesis of α,α-Diaryl α-Amino Esters via Bi(V)-Mediated Arylation/S_N2-Displacement of Kukhtin–Ramirez Intermediates

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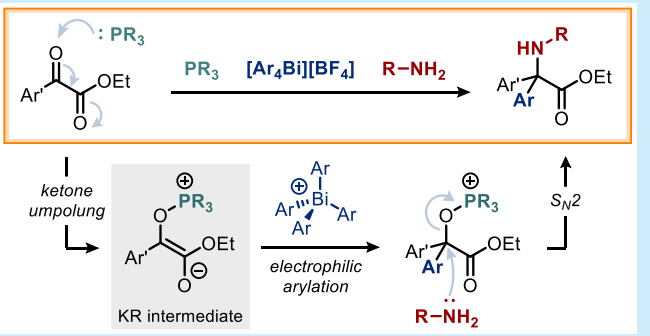
ABSTRACT: We report a concise and modular approach to α,α-diaryl α-amino esters from readily available α-keto esters. This mild, one-pot protocol proceeds via ketone umpolung, with *in situ* formation of a Kukhtin–Ramirez intermediate preceding sequential electrophilic arylation by Bi(V) and S_N2 displacement by an amine. The methodology is compatible with a wide range of anilines and primary amines - including derivatives of drugs and proteinogenic amino acids - Bi(V) arylating agents, and α-keto ester substrates.



Quaternary amino acids possess enhanced chemical and metabolic stability, greater lipophilicity, and distinct conformational preferences relative to the canonical amino acids.[1−4] As such, quaternary amino acids have been used widely in the investigation of peptide structure and biological activity, the rational design of foldamers,[1] and the development of peptoid-based therapeutics.[5,6] While α,α-dialkyl substitution is typically associated with the nucleation and stabilization of a helical secondary structure,[1,7,8] α,α-diaryl amino acids exhibit a context-dependent conformational preference that often favors extended geometries.[9−13] The complementary conformational properties and chemical characters (*i.e.*, lipophilic vs aromatic) of these two classes of quaternary amino acids makes them individually valuable to peptide design and, therefore, important targets for chemical synthesis.

α,α-Diaryl amino acids can be disconnected via any one of the four bonds to the quaternary center. Despite the diversity of approaches—which include amination,[14−18] arylation,[19−31] and carboxylation[32] with both electrophilic and nucleophilic reagents—the vast majority are united by a common feature: only one bond to the quaternary center is disconnected in each retrosynthetic operation. The synthesis of α,α-diaryl amino acids therefore typically requires multiple steps, which ultimately reduces their efficiency. Strategies that simultaneously disconnect two or more bonds to the quaternary center are currently limited to Greaney's tandem S_N2/Smiles arylation methodology (Scheme 1A, top).[33] While an important conceptual advance, the scope and practicality of this approach are inherently limited by the need for electron-poor aryl partners, and the fact that both the aryl and the nitrogen components originate from a single sulfonamide precursor. There thus remains an unmet need for a more general and convergent route to α,α-diaryl amino acids in which each fragment is derived from separate sources.

Herein we demonstrate a novel two-bond disconnection that allows for the modular assembly of α,α-diaryl α-amino acids in a single step from independently variable reagents (Scheme 1A, bottom). Installation of diverse aryl and amino components at the quaternary center is achieved via net deoxygenation of an α-keto ester core. The methodology proceeds under mild conditions and tolerates synthetically valuable functionality, such as esters, alkenes, alkynes, and aryl bromides.

We recognized that the formal polarity inversion of α-keto esters **1** can be achieved by addition of a nucleophilic phosphine to form the corresponding Kukhtin–Ramirez (KR) intermediate **2** (Scheme 1B).[34] While interception of KR-type intermediates has been demonstrated with numerous electrophiles,[34−38] electrophilic arylation has never been reported. We envisaged that **2a**, the phosphonium enolate isomer of the KR intermediate, would react with tetraarylbismuthonium reagents **3**[39−42] to form electrophilic alkoxyphosphonium salt **4**. Subsequent displacement of phosphine oxide by a nitrogen nucleophile would complete the sequence, ultimately providing concise and modular access to the desired α,α-diaryl α-amino acid derivative **5**. While S_N2 reactions at quaternary centers are typically very rare, such substitutions α to esters are facilitated

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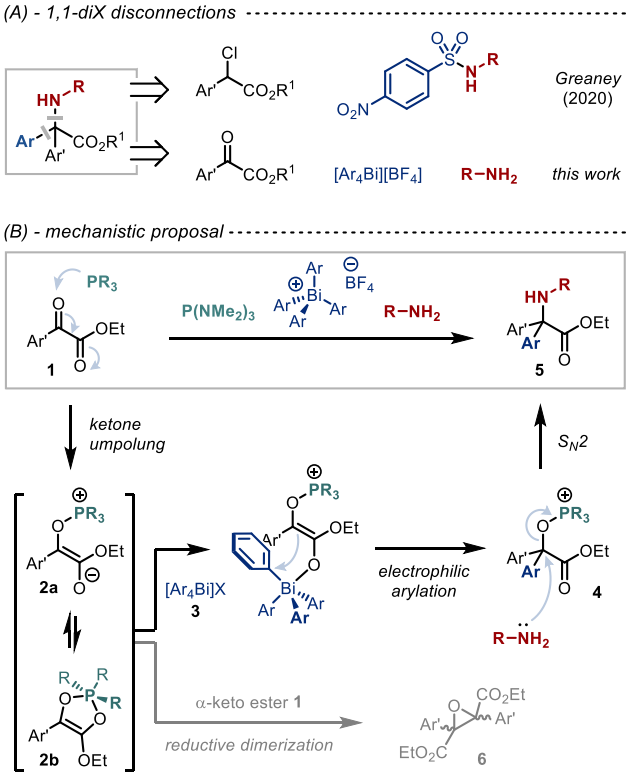
Scheme 1. Strategies for the Synthesis of α,α-Diaryl Amino Esters



by the planar and electron-withdrawing nature of the adjacent carbonyl moiety.[43−48]

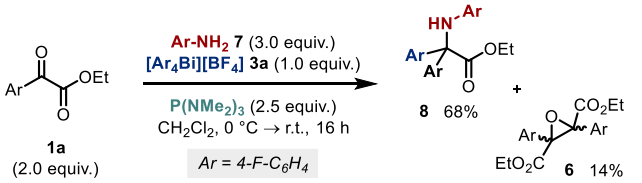
Overall, this strategy introduces the aryl group and the amine moiety in the same synthetic step, but from different sources and without the need of prefunctionalization of the starting materials. Crucial to success is (1) avoiding competitive reductive dimerization of the α-keto ester that affords epoxide **6**, (2) use of a Bi(V) reagent with a non-nucleophilic counterion to avoid competitive attack on **4**, and (3) chemo-compatibility between a nucleophilic amine and an electrophilic Bi(V) species.

Key steps toward the implementation of the proposed three-component amino arylation reaction are summarized in Table 1. Ultimately, rigorous optimization (see the Supporting Information) revealed that dropwise addition of $P(NMe_2)_3$ over 1 min to a solution of α-keto ester **1a**, tetraarylbismuthonium salt **3a**, and aniline **7** at 0 °C, followed by stirring for 16 h at room temperature, gave the amino-arylated product **8** in reproducibly high yields (Table 1, entry 1).

Neither PPh_3, $P(n\text{-}Bu)_3$, nor $P(OEt)_3$ (Table 1, entry 2) proved to be a competent alternative to $P(NMe_2)_3$. This is consistent with Ramirez's observation that formation of the oxyphosphonium enolate **2a** (Scheme 1B) is favored for phosphines that are sterically bulky and highly nucleophilic, such as $P(NMe_2)_3$,[49−51,37] whereas smaller phosphines favor formation of phospholene **2b** while less nucleophilic phosphines are unreactive.[50,52,53] Importantly, a control reaction demonstrated the key role of the phosphine in promoting the desired reactivity (entry 3).

Although the yield of amino acid **8** decreased significantly when $P(NMe_2)_3$ was added at either lower or higher temperatures, a comparable yield was obtained at room temperature (Table 1, entries 4−6). Furthermore, an assessment of different solvents revealed that relatively polar media are required (entries 7 and 8). The observed sensitivity of the reaction may reflect the fact that the distribution of the KR intermediate between the isomeric phosphonium enolate **2a** and dioxaphospholene **2b** forms (Scheme 1B) depends strongly on reaction conditions.[54−56] Indeed, detailed VT-NMR studies have shown a delicate correlation between the speciation of KR intermediates—which ultimately controls product distribution—and the properties of the phosphine, solvent, and temperature.[57]

Table 1. Summary of Reaction Optimization[a]



Entry	Deviation from Above	% 8	% 6
1	equiv: **1a** (1.5), **7** (1.5), **3a** (1.0), $P(NMe_2)_3$ (2.0)	80	3
2	PPh_3/$P(n\text{-}Bu)_3$/$P(OEt)_3$	<5	0
3	no phosphine	<5	0
4	−78 °C → rt	64	18
5	rt	70	3
6	40 °C	61	5
7	THF	56	7
8	toluene	<5	0
9	**1a** added last	35	6
10	**1a** added over 1 h, $[\mathbf{3a}]_0$ = 0.2 M	<5	0
11	$P(NMe_2)_3$ added over 1 h	<5	0

[a]Reactions performed on a 0.1 mmol scale using anhydrous CH_2Cl_2 ($[\mathbf{3a}]_0$ = 0.1 M). Yields determined by ^{19}F NMR spectroscopic analysis vs internal standard ($PhCF_3$); yields of epoxide **6** are calculated relative to α-keto ester **1a**.

To suppress the formation of epoxide **6**,[38,37,57] which was consistently observed as a side product during optimization, the order and rate of reagent addition was investigated. However, the yield of amino acid **8** was significantly reduced when α-keto ester **1a** was added as the last component, or when either **1a** or $P(NMe_2)_3$ were added over 1 h (entries 9−11). In contrast, the use of more economic stoichiometries of **1a**, **7**, and $P(NMe_2)_3$ (added over 1 min) afforded amino acid **8** in high yield and reduced the formation of epoxide **6** to <5% (entry 1).

Having identified suitable conditions, the scope and limitations of the methodology were investigated (Scheme 2). Variation of the amine nucleophile revealed that electronically (**8**−**14**) and sterically (**15**) diverse anilines afford the corresponding amino acids in high yields (Scheme 2A). The reaction is compatible with synthetically versatile aryl bromides (**13**) and potentially sensitive functional groups such as esters (**11**) and terminal alkynes (**14**).

In all cases, the triarylbismuth co-product can be isolated in >95% yield during product purification (Scheme 2, top). Converting this recovered material back into the corresponding bismuthonium salt (see the Supporting Information) reduces the waste that would otherwise be associated with the use of these reagents.

The methodology is equally applicable to primary amine nucleophiles (Scheme 2B) bearing linear aliphatic (**16**−**20**), benzylic (**21**−**24**), and α-branched (**25**) substituents. The functional group tolerance includes alkenes (**17**) and both

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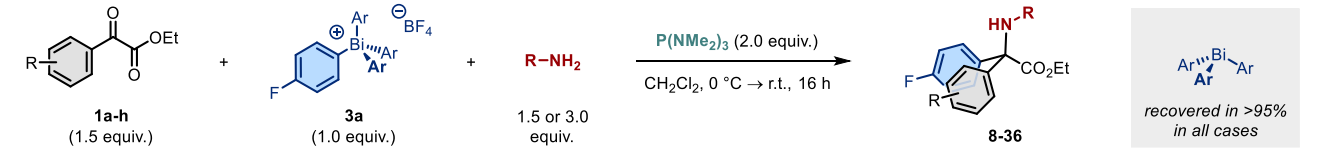
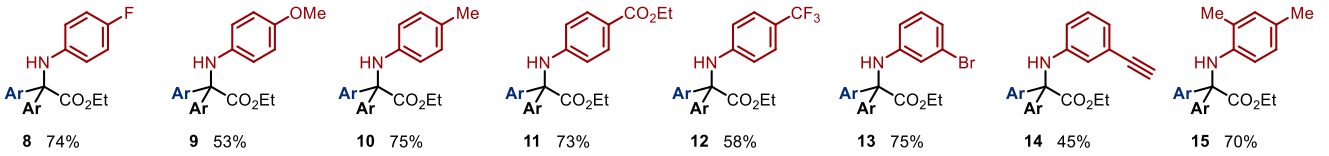
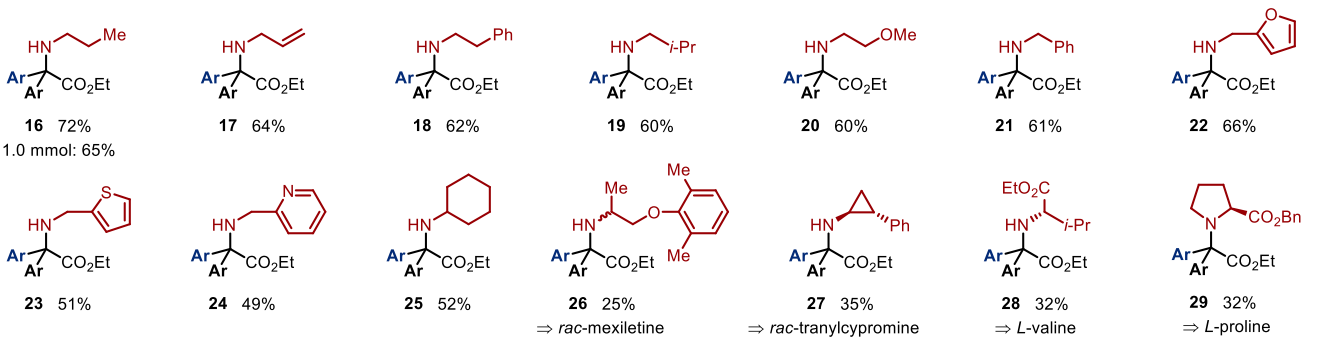
Scheme 2. Scope with Respect to Amine Nucleophile and α-Keto Ester Substrate[a]



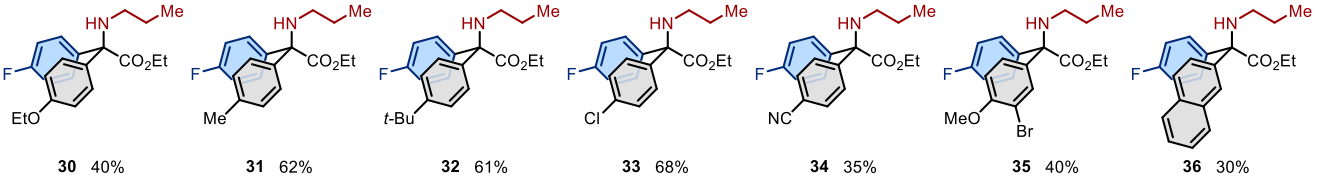
(A) - scope of anilines (Ar = 4-F-C6H4)



(B) - scope of primary amines (Ar = 4-F-C6H4)



(C) - scope of α–keto esters



[a]Reactions performed on a 0.5 mmol scale using anhydrous CH_2Cl_2 ($[\mathbf{3a}]_0$ = 0.1 M) and either 1.5 equiv of aniline nucleophile or 3.0 equiv of aliphatic amine nucleophile. Yields refer to material isolated after purification.

electron-rich and electron-poor heterocycles (**22**–**24**). Significantly, a variety of complex amines derived from natural products and pharmaceutical compounds can be employed, affording amino acid conjugates of *rac*-mexiletine (**26**) and *rac*-tranylcypromine (**27**). The use of proteinogenic amino acids as the nucleophile generates *N*-linked dipeptides (**28**, **29**), a motif that forms the core of several highly successful ACE inhibitors—including enalapril, lisinopril, and benazepril[58,59]—and the opine family of natural products.[60,61] The lower yield obtained for structurally complex amines presumably reflects the steric demands of the reaction, which requires an S_N2 substitution at a quaternary center (Scheme 1B).

Variation of the α-keto ester counterpart revealed a significant sensitivity toward the identity of the substrate (Scheme 2C). Thus, while moderately electron-donating and -withdrawing substituents are well accommodated (**31**–**33**), lower yields are obtained at either electronic extreme (**30**, **34**).

A particular benefit of the present three-component strategy is that it allows any given aryl group to be introduced from either the α-keto ester or the bismuthonium salt, such that two distinct disconnections are viable for each amino acid target (Scheme 3). The practicality of this retrosynthetic flexibility is illustrated in the comparable yields obtained across three target compounds, irrespective of the combination of aryl moieties or the disconnection employed. Notably, this series of studies also demonstrates the scope with respect to the bismuthonium salt, which spans from electron poor (**33**, *disconnection 2*) to electron rich (**37**, *disconnection 2*).

Finally, we sought to extend our methodology to the synthesis of *N*-unsubstituted amino acids of type **38** (Scheme 4), a potentially valuable building block for drug discovery.[62,63] Gratifyingly, **38** can either be accessed directly by simply using a solution of ammonia as the nitrogen nucleophile (*path i*) or indirectly *via* deprotection of the corresponding *N*-benzyl (*path ii*), *N*-*p*-methoxyphenyl (*path iii*), or *N*-allyl (*path iv*) amino esters.[64]

In summary, we have developed a modular and versatile approach to α,α-diaryl α-amino esters in which two bonds to the quaternary center are formed in a single operation. Net deoxygenation of an α-keto ester substrate is achieved by reaction of the umpoled Kukhtin–Ramirez intermediate with an electrophilic Bi(V) arylating agent, prior to S_N2-displacement of the resulting alkoxyphosphonium intermediate by an

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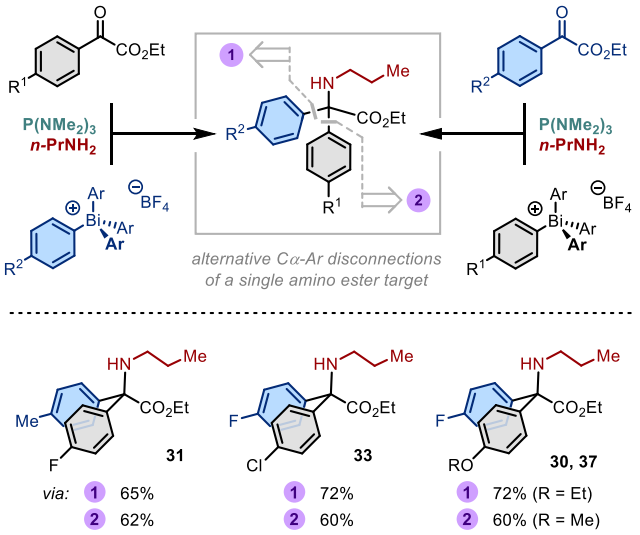
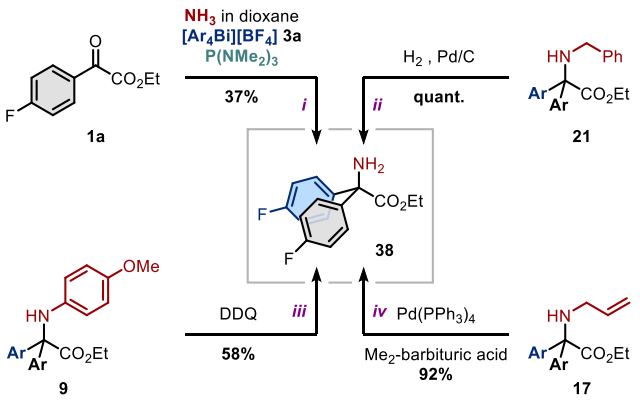
Scheme 3. Comparison of C_{quat}–Ar Disconnections[a]



[a]Reactions performed on a 0.5 mmol scale using anhydrous CH_2Cl_2 ($[3]_0$ = 0.1 M); yields determined by ^{19}F NMR spectroscopic analysis vs internal standard ($PhCF_3$).

Scheme 4. Synthesis of Primary Amino Esters[a]



[a]See the Supporting Information for full experimental details.

amine nucleophile. Each of the three components can be varied independently, giving concise access to diverse amino esters featuring synthetically valuable functionality. The scope with respect to the amine nucleophile includes both anilines and aliphatic amines; use of biologically relevant amine nucleophiles affords new drug conjugates and N-linked dipeptides, whereas the use of ammonia provides direct access to a key primary amino acid building block.

■ ASSOCIATED CONTENT

Supporting Information

The data underlying this study are available in the published article and its online Supporting Information. The Supporting Information is available free of charge on the ACS Publications Web site: Experimental procedures, spectra, and optimization data (PDF) FAIR Data, including the primary NMR FID files for the following compounds: **1a**, **1c**, **1g**, **1h**, **3a–3d**, **8–38** and triarylbismuthines. The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03201.

Experimental procedures, spectra, and optimization data (PDF)

FAIR data, including the primary NMR FID files, for compounds **3a–3d** (ZIP)

FAIR data, including the primary NMR FID files, for compounds **8–12** (ZIP)

FAIR data, including the primary NMR FID files, for compounds **13–17** (ZIP)

FAIR data, including the primary NMR FID files, for compounds **18–22** (ZIP)

FAIR data, including the primary NMR FID files, for compounds **23–27** (ZIP)

FAIR data, including the primary NMR FID files, for compounds **28–32** (ZIP)

FAIR data, including the primary NMR FID files, for compounds **33–38** (ZIP)

FAIR data, including the primary NMR FID files, for compounds Bi compounds (ZIP)

FAIR data, including the primary NMR FID files, for compounds keto esters (ZIP)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. Design of Folded Peptides. *Chem. Rev.* **2001**, *101* (10), 3131–3152.

(2) Tanaka, M. Design and Synthesis of Chiral Alpha,Alpha-Disubstituted Amino Acids and Conformational Study of Their Oligopeptides. *Chem. Pharm. Bull.* **2007**, *55* (3), 349–358.

(3) Revilla-López, G.; Torras, J.; Curcó, D.; Casanovas, J.; Calaza, M. I.; Zanuy, D.; Jiménez, A. I.; Cativiela, C.; Nussinov, R.; Grodzinski, P.; Alemán, C. NCAD, a Database Integrating the Intrinsic Conformational Preferences of Non-Coded Amino Acids. *J. Phys. Chem. B* **2010**, *114* (21), 7413–7422.

(4) Toniolo, C.; Formaggio, F.; Kaptein, B.; Broxterman, Q. B. You Are Sitting on a Gold Mine! *Synlett* **2006**, *2006* (09), 1295−1310.
(5) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. Control of Peptide Conformation by the Thorpe-Ingold Effect (Cα-Tetrasubstitution). *Pept. Sci.* **2001**, *60* (6), 396−419.
(6) Meusel, M.; Gütschow, M. RECENT DEVELOPMENTS IN HYDANTOIN CHEMISTRY. A REVIEW. *Org. Prep. Proced. Int.* **2004**, *36* (5), 391−443.
(7) Kaul, R.; Balaram, P. Stereochemical Control of Peptide Folding. *Bioorg. Med. Chem.* **1999**, *7* (1), 105−117.
(8) Karle, I. L.; Balaram, P. Structural Characteristics of Alpha-Helical Peptide Molecules Containing Aib Residues. *Biochemistry* **1990**, *29* (29), 6747−6756.
(9) Casanovas, J.; Zanuy, D.; Nussinov, R.; Alemán, C. Intrinsic Conformational Characteristics of α,α-Diphenylglycine. *J. Org. Chem.* **2007**, *72* (6), 2174−2181.
(10) Zanuy, D.; Rodríguez-Ropero, F.; Nussinov, R.; Alemán, C. Testing β-Helix Terminal Coils Stability by Targeted Substitutions with Non-Proteogenic Amino Acids: A Molecular Dynamics Study. *J. Struct. Biol.* **2007**, *160* (2), 177−189.
(11) Pavone, V.; Lombardi, A.; Saviano, M.; Nastri, F.; Zaccaro, L.; Maglio, O.; Pedone, C.; Omote, Y.; Yamanaka, Y.; Yamada, T. Conformational Behaviour of Cα,α-Diphenylglycine: Folded vs. Extended Structures in DϕG-Containing Tripeptides. *J. Pept. Sci.* **1998**, *4* (1), 21−32.
(12) Pavone, V.; Lombardi, A.; Saviano, M.; De Simone, G.; Nastri, F.; Maglio, O.; Omote, Y.; Yamanaka, Y.; Yamada, T. Conformational Behavior of Cα,α-Diphenyl Glycine: Extended Conformation in Tripeptides Containing Consecutive Dϕg Residues. *Biopolymers* **2000**, *53* (2), 161−168.
(13) Castro, T. G.; Micaêlo, N. M. Modeling of Peptaibol Analogues Incorporating Nonpolar α,α-Dialkyl Glycines Shows Improved α-Helical Preorganization and Spontaneous Membrane Permeation. *J. Phys. Chem. B* **2014**, *118* (3), 649−658.
(14) Yang, C.; Liu, Y.; Yang, J.-D.; Li, Y.-H.; Li, X.; Cheng, J.-P. Amination of 3-Substituted Benzofuran-2(3H)-Ones Triggered by Single-Electron Transfer. *Org. Lett.* **2016**, *18* (5), 1036−1039.
(15) Benavent, L.; Baeza, A.; Freckleton, M. Chiral 2-Aminobenzimidazole as Bifunctional Catalyst in the Asymmetric Electrophilic Amination of Unprotected 3-Substituted Oxindoles. *Molecules* **2018**, *23* (6), 1374.
(16) Paria, S.; Kang, Q.-K.; Hatanaka, M.; Maruoka, K. Design of Efficient Chiral Bifunctional Phase-Transfer Catalysts Possessing an Amino Functionality for Asymmetric Aminations. *ACS Catal.* **2019**, *9* (1), 78−82.
(17) Ishihara, K.; Hamamoto, H.; Matsugi, M.; Shioiri, T. SN2 Displacement at the Quaternary Carbon Center: A Novel Entry to the Synthesis of α,α-Disubstituted α-Amino Acids. *Tetrahedron Lett.* **2015**, *56* (23), 3169−3171.
(18) Yin, X.-P.; Zhu, L.; Zhou, J. Metal-Free Azidation of α-Hydroxy Esters and α-Hydroxy Ketones Using Azidotrimethylsilane. *Adv. Synth. Catal.* **2018**, *360* (6), 1116−1122.
(19) Liu, X.; Hartwig, J. F. Palladium-Catalyzed α-Arylation of Azlactones to Form Quaternary Amino Acid Derivatives. *Org. Lett.* **2003**, *5* (11), 1915−1918.
(20) Penso, M.; Albanese, D.; Landini, D.; Lupi, V.; Tagliabue, A. Complementary Heterogeneous/Homogeneous Protocols for the Synthesis of Densely Functionalized Benzo[d]Sultams: C−C Bond Formation by Intramolecular Nucleophilic Aromatic Fluorine Displacement. *J. Org. Chem.* **2008**, *73* (17), 6686−6690.
(21) Foschi, F.; Tagliabue, A.; Mihali, V.; Pilati, T.; Pecnikaj, I.; Penso, M. Memory of Chirality Approach to the Enantiodivergent Synthesis of Chiral Benzo[d]Sultams. *Org. Lett.* **2013**, *15* (14), 3686−3689.
(22) Chai, Z.; Wang, B.; Chen, J.-N.; Yang, G. Arylation of Azlactones Using Diaryliodonium Bromides and Silver Carbonate: Facile Access to α-Tetrasubstituted Amino Acid Derivatives. *Adv. Synth. Catal.* **2014**, *356* (11−12), 2714−2718.
(23) Leonard, D. J.; Ward, J. W.; Clayden, J. Asymmetric α-Arylation of Amino Acids. *Nature* **2018**, *562* (7725), 105−109.
(24) Hata, S.; Koyama, H.; Shimizu, M. Synthesis of α,α-Disubstituted α-Amino Esters: Nucleophilic Addition to Iminium Salts Generated from Amino Ketene Silyl Acetals. *J. Org. Chem.* **2011**, *76* (23), 9670−9677.
(25) Wang, H.; Jiang, T.; Xu, M.-H. Simple Branched Sulfur−Olefins as Chiral Ligands for Rh-Catalyzed Asymmetric Arylation of Cyclic Ketimines: Highly Enantioselective Construction of Tetrasubstituted Carbon Stereocenters. *J. Am. Chem. Soc.* **2013**, *135* (3), 971−974.
(26) Takechi, R.; Nishimura, T. Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids to Cyclic N-Sulfonyl Ketimines towards the Synthesis of α,α-Diaryl-α-Amino Acid Derivatives. *Org. Biomol. Chem.* **2015**, *13* (17), 4918−4924.
(27) Zhou, B.; Li, K.; Jiang, C.; Lu, Y.; Hayashi, T. Modified Amino Acid-Derived Phosphine-Imine Ligands for Palladium-Catalyzed Asymmetric Arylation of Cyclic N-Sulfonyl Imines. *Adv. Synth. Catal.* **2017**, *359* (11), 1969−1975.
(28) Zhao, Y.; Cai, L.; Huang, T.; Meng, S.; Chan, A. S. C.; Zhao, J. Solvent-Mediated C3/C7 Regioselective Switch in Chiral Phosphoric Acid-Catalyzed Enantioselective Friedel-Crafts Alkylation of Indoles with α-Ketiminoesters. *Adv. Synth. Catal.* **2020**, *362* (6), 1309−1316.
(29) Qiu, Z.; Li, Y.; Zhang, Z.; Teng, D. Spiro Indane-Based Phosphine−Oxazoline Ligands for Palladium-Catalyzed Asymmetric Arylation of Cyclic N-Sulfonyl Imines. *Transit. Met. Chem.* **2019**, *44* (7), 649−654.
(30) Xue, F.; Liu, Q.; Zhu, Y.; Huang, Y.; Ge, J.; Wan, B. Highly Enantioselective Rh-Catalyzed Arylation of N,N-Dimethylsulfamoyl-Protected Aldimines and Cyclic N-Sulfonylimines with Chiral Phenyl Backbone Sulfoxide-Olefin Ligands. *Synthesis* **2020**, *52* (10), 1498−1511.
(31) Tsuji, T.; Tanaka, T.; Tanaka, T.; Yazaki, R.; Ohshima, T. Catalytic Aerobic Cross-Dehydrogenative Coupling of Azlactones En Route to α,α-Disubstituted α-Amino Acids. *Org. Lett.* **2020**, *22* (11), 4164−4170.
(32) Ju, T.; Fu, Q.; Ye, J.-H.; Zhang, Z.; Liao, L.-L.; Yan, S.-S.; Tian, X.-Y.; Luo, S.-P.; Li, J.; Yu, D.-G. Selective and Catalytic Hydrocarboxylation of Enamides and Imines with CO2 to Generate α,α-Disubstituted α-Amino Acids. *Angew. Chem., Int. Ed.* **2018**, *57* (42), 13897−13901.
(33) Johnson, S.; Kovács, E.; Greaney, M. F. Arylation and Alkenylation of Activated Alkyl Halides Using Sulfonamides. *Chem. Commun.* **2020**, *56* (21), 3222−3224.
(34) Liu, Y.; Sun, F.; He, Z. Recent Renewed Interest in the Classical Kukhtin-Ramirez Adducts. *Tetrahedron Lett.* **2018**, *59* (47), 4136−4148.
(35) Corre, E.; Foucaud, A. Synthesis of 2-Acetyl-3-Aryl-1,1-Dicyano-2-Methyl-Cyclopropanes. *J. Chem. Soc. D, Chem. Commun.* **1971**, *11*, 570a.
(36) Wilson, E. E.; Rodriguez, K. X.; Ashfeld, B. L. Stereochemical Implications in the Synthesis of 3,3′-Spirocyclopropyl Oxindoles from β-Aryl/Alkyl-Substituted Alkylidene Oxindoles. *Tetrahedron* **2015**, *71* (35), 5765−5775.
(37) Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. A Nonmetal Approach to α-Heterofunctionalized Carbonyl Derivatives by Formal Reductive X-H Insertion. *Angew. Chem., Int. Ed.* **2012**, *51* (42), 10605−10609.
(38) Wang, S. R.; Radosevich, A. T. P(NMe2)3-Mediated Umpolung Alkylation and Nonylidic Olefination of α-Keto Esters. *Org. Lett.* **2015**, *17* (15), 3810−3813.
(39) Barton, D. H. R.; Charpiot, B.; Motherwell, W. B. Regiospecific Arylation by Acid/Base Controlled Reactions of Tetraphenylbismuth Esters. *Tetrahedron Lett.* **1982**, *23* (33), 3365−3368.
(40) Barton, D. H. R.; Blazejewski, J.-C.; Charpiot, B.; Finet, J.-P.; Motherwell, W. B.; Papoula, M. T. B.; Stanforth, S. P. Pentavalent Organobismuth Reagents. Part 3. Phenylation of Enols and of Enolate and Other Anions. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2667−2675.

https://doi.org/10.1021/acs.orglett.2c03201
Org. Lett. 2022, 24, 8002−8007

(41) Ooi, T.; Goto, R.; Maruoka, K. Fluorotetraphenylbismuth: A New Reagent for Efficient Regioselective α-Phenylation of Carbonyl Compounds. *J. Am. Chem. Soc.* **2003**, *125* (35), 10494−10495.
(42) Gagnon, A.; Dansereau, J.; Le Roch, A. Organobismuth Reagents: Synthesis, Properties and Applications in Organic Synthesis. *Synthesis* **2017**, *49* (8), 1707−1745.
(43) Clayden, J.; MacLellan, P. Asymmetric Synthesis of Tertiary Thiols and Thioethers. *Beilstein J. Org. Chem.* **2011**, *7*, 582−595.
(44) Lanke, V.; Marek, I. Stereospecific Nucleophilic Substitution at Tertiary and Quaternary Stereocentres. *Chem. Sci.* **2020**, *11* (35), 9378−9385.
(45) Ikegai, K.; Pluempanupat, W.; Mukaiyama, T. Preparation of Tert-Alkyl Aryl Sulfides from Tert-Alcohols via Quinone-Mediated Oxidation−Reduction Condensation between Tert-Alkyl Diphenylphosphinites and 2-Sulfanyl-1,3-Benzothiazole. *Chem. Lett.* **2005**, *34* (5), 638−639.
(46) Kuroda, K.; Maruyama, Y.; Hayashi, Y.; Mukaiyama, T. Stereospecific Synthesis of Alkyl Aryl Sulfides from Alcohols and 2-Sulfanylbenzothiazole Using Aryl Diphenylphosphinite and Azide Compounds by a New Type of Oxidation−Reduction Condensation. *Chem. Lett.* **2008**, *37* (8), 836−837.
(47) Shibatomi, K.; Soga, Y.; Narayama, A.; Fujisawa, I.; Iwasa, S. Highly Enantioselective Chlorination of β-Keto Esters and Subsequent SN2 Displacement of Tertiary Chlorides: A Flexible Method for the Construction of Quaternary Stereogenic Centers. *J. Am. Chem. Soc.* **2012**, *134* (24), 9836−9839.
(48) Shibatomi, K.; Kotozaki, M.; Sasaki, N.; Fujisawa, I.; Iwasa, S. Williamson Ether Synthesis with Phenols at a Tertiary Stereogenic Carbon: Formal Enantioselective Phenoxylation of β-Keto Esters. *Chem. − A Eur. J.* **2015**, *21* (40), 14095−14098.
(49) Ramirez, F.; Dershowitz, S. Reaction of Trialkyl Phosphites and of Triaryl Phosphites with Chloranil. A New Synthesis of Hydroquinone Monoalkyl Ethers. *J. Am. Chem. Soc.* **1959**, *81* (3), 587−590.
(50) Ramirez, F.; Patwardhan, A. V.; Kugler, H. J.; Smith, C. P. Formation of Phosphorus-Oxygen Bonds in the Reactions of Triaminophosphines with o-Quinones, Vicinal Triketones, and Xoxmalonic Esters. Triaminooxyphosphonium Dipolar Ions and Triaminodioxaphosphoranes. Phosphorus-31 Nuclear Magnetic Resonance Spectra. *J. Am. Chem. Soc.* **1967**, *89* (24), 6276−6282.
(51) Lin, Y. C.; Gilhula, J. C.; Radosevich, A. T. Nontrigonal Constraint Enhances 1,2-Addition Reactivity of Phosphazenes. *Chem. Sci.* **2018**, *9* (18), 4338−4347.
(52) Ramirez, F.; Desai, N. B. Organic Compounds with Pentavalent Phosphorus. VIII. Cyclic Unsaturated Oxyphosphoranes from the Reaction of Tertiary Phosphite Esters with o-Quinones and with α-Diketones. *J. Am. Chem. Soc.* **1963**, *85* (20), 3252−3258.
(53) Tolman, C. A. Steric Effects of Phosphorus Ligands in Organometallic Chemistry and Homogeneous Catalysis. *Chem. Rev.* **1977**, *77* (3), 313−348.
(54) Denney, D. B.; Denney, D. Z.; Hammond, P. J.; Tseng, K.-S. Structures of Some Condensation Products of Alpha-Dicarbonyl Compounds and Tris(Amino)Phosphines in Solution. *J. Am. Chem. Soc.* **1981**, *103* (8), 2054−2057.
(55) Ramirez, F.; Gulati, A. S.; Smith, C. P. Reaction of Tris(Dialkylamino)Phosphines with Aromatic Aldehydes. I. Nitrobenzaldehydes. Formation of 2,2,2-Triamino-1,3,2-Dioxaphospholanes and Their Conversion into Epoxides. *J. Org. Chem.* **1968**, *33* (1), 13−19.
(56) Ramirez, F. Oxyphosphoranes. *Acc. Chem. Res.* **1968**, *1* (6), 168−174.
(57) Gulotty, E. M.; Rodriguez, K. X.; Parker, E. E.; Ashfeld, B. L. Oxyphosphonium Enolate Equilibria in a (4 + 1)-Cycloaddition Approach toward Quaternary C3-Spirooxindole Assembly. *Chem. − A Eur. J.* **2021**, *27* (40), 10349−10355.
(58) Patchett, A. A.; Harris, E.; Tristram, E. W.; Wyvratt, M. J.; Wu, M. T.; Taub, D.; Peterson, E. R.; Ikeler, T. J.; ten Broeke, J.; Payne, L. G.; Ondeyka, D. L.; Thorsett, E. D.; Greenlee, W. J.; Lohr, N. S.; Hoffsommer, R. D.; Joshua, H.; Ruyle, W. V.; Rothrock, J. W.; Aster, S. D.; Maycock, A. L.; Robinson, F. M.; Hirschmann, R.; Sweet, C. S.; Ulm, E. H.; Gross, D. M.; Vassil, T. C.; Stone, C. A. A New Class of Angiotensin-Converting Enzyme Inhibitors. *Nature* **1980**, *288* (5788), 280−283.
(59) Patchett, A. A. The Chemistry of Enalapril. *Br. J. Clin. Pharmacol.* **1984**, *18* (S2), 201S−207S.
(60) Albat, D.; Neudörfl, J.-M.; Schmalz, H.-G. A General Stereocontrolled Synthesis of Opines through Asymmetric Pd-Catalyzed N-Allylation of Amino Acid Esters. *Eur. J. Org. Chem.* **2021**, *2021* (14), 2099−2102.
(61) Hyslop, J. F.; Lovelock, S. L.; Watson, A. J. B.; Sutton, P. W.; Roiban, G.-D. N-Alkyl-α-Amino Acids in Nature and Their Biocatalytic Preparation. *J. Biotechnol.* **2019**, *293*, 56−65.
(62) Konnert, L.; Reneaud, B.; de Figueiredo, R. M.; Campagne, J.-M.; Lamaty, F.; Martinez, J.; Colacino, E. Mechanochemical Preparation of Hydantoins from Amino Esters: Application to the Synthesis of the Antiepileptic Drug Phenytoin. *J. Org. Chem.* **2014**, *79* (21), 10132−10142.
(63) Groutas, W. C.; Kuang, R. Z.; Venkataraman, R. Substituted 3-Oxo-1,2,5-Thiadiazolidine 1,1-Dioxides: A New Class of Potential Mechanism-Based Inhibitors of Human Leukocyte Elastase and Cathepsin G. *Biochem. Biophys. Res. Commun.* **1994**, *198* (1), 341−349.
(64) Greene, T. W.; Wuts, P. G. M. Protection for the Amino Group. In *Greene's Protective Groups in Organic Synthesis*; John Wiley & Sons, Inc.: Hoboken, 2006; pp 696−926. DOI: 10.1002/9780470053485.ch7.

https://doi.org/10.1021/acs.orglett.2c03201
Org. Lett. 2022, 24, 8002−8007