doi.org/10.1002/adsc.202200716
Advanced Synthesis & Catalysis

Very Important Publication

Radical C–H Alkylation with Ethers and Unactivated Cycloalkanes toward the Assembly of Tetrasubstituted Amino Acid Derivatives

Marcos San Segundo[a] and Arkaitz Correa[a,*]

[a] University of the Basque Country (UPV/EHU), Department of Organic Chemistry I, Joxe Mari Korta R&D Center, Avda. Tolosa 72, 20018 Donostia-San Sebastián (Spain)
E-mail: arkaitz.correa@ehu.eus

Manuscript received: June 30, 2022; Revised manuscript received: August 2, 2022;
Version of record online: August 24, 2022

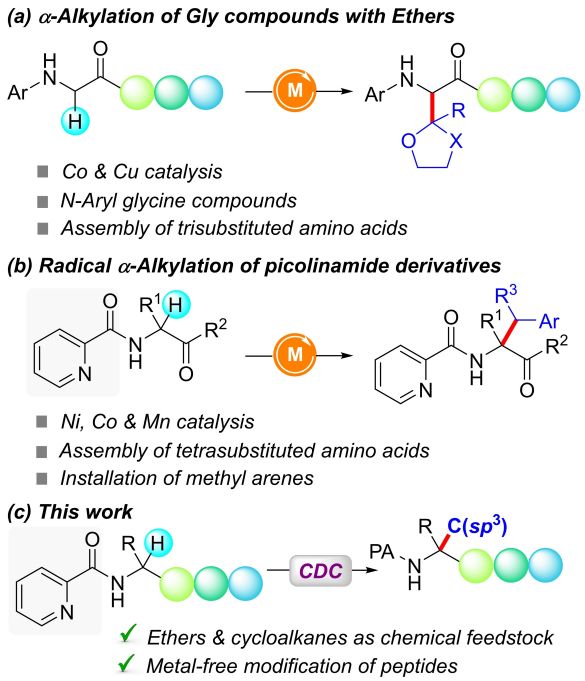
Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202200716

Abstract: A radical α–C–H alkylation of a collection of *N*-picolinamide amino acid derivatives with ethers and cycloalkanes as chemical feedstock is described. This cross-dehydrogenative coupling is distinguished by its reliable scalability and removable auxiliary group, and enables the assembly of a variety of tri- and tetrasubstituted amino acid compounds.

Keywords: alkylation; amino acid; cross-dehydrogenative coupling; peptides; C–H functionalization

Owing to their chemical inertness, ethers such as tetrahydrofuran, 1,4-dioxane and diethyl ether have been traditionally employed as common solvents in organic synthesis. However, the last decade has witnessed the upsurge of a myriad of C(sp^3)–H functionalization reactions featuring ethers[1] as abundant, yet low-cost chemical feedstocks, thereby providing α-branched ethers which are prevalent motifs in a vast array of biologically relevant molecules and FDA-approved drugs.[2] The foremost strategy involves the homolytic cleavage of the α-C(sp^3)–H bonds adjacent to the oxygen atom, thus resulting in transient carbon-centered radicals prone to undergo a subsequent oxidative coupling process. Likewise, unactivated hydrocarbons stand out as privileged counterparts that can participate in these processes following a similar reaction pathway.[3] Despite the wealth of reports, the coupling of two distinct C(sp^3)–H backbones still represents a great challenge because often a dual activation is required.

Amino acids are highly coveted compounds and their modification in a site-selective fashion poses a prime scientific goal at the forefront of chemical biology and organic chemistry.[4] Metal catalysis has recently unlocked new paradigms in the field and enabled the appendance of numerous functional groups within the amino acid backbone[5] as well as the side-chains of the corresponding peptides.[6] Since the pioneering work by Li on the cross-dehydrogenative coupling (CDC) of amino acid derivatives,[7] this tactic has evolved into a reliable platform to forge new C(sp^3)–C and C(sp^3)-heteroatom bonds within a peptide setting.[8] Of particular importance is the radical α-alkylation of terminal *N*-aryl glycine derivatives in the presence of copper[9] and cobalt catalysts[10] with simple ethers to assemble new trisubstituted amino acid derivatives (Scheme 1a). As the majority of the CDCs,[5] the presence of a terminal *N*-aryl group is required,[11] which is not easily removed, and the process is only applicable within unsubstituted glycine units. These synthetic downsides were overcome by the elegant approach by You,[12] wherein a removable picolinamide group enabled not only the modification of glycine but also its challenging substituted congeners to produce α,α-disubstituted amino ester compounds. This chelation-assisted protocol allowed for the installation of nucleophilic indoles[12d] and malonates[12b,d] as well as free radical species derived from methyl arenes[12a,c] (Scheme 1b). However, it remains an underdeveloped platform with untapped potential for creating molecular diversity. Inspired by



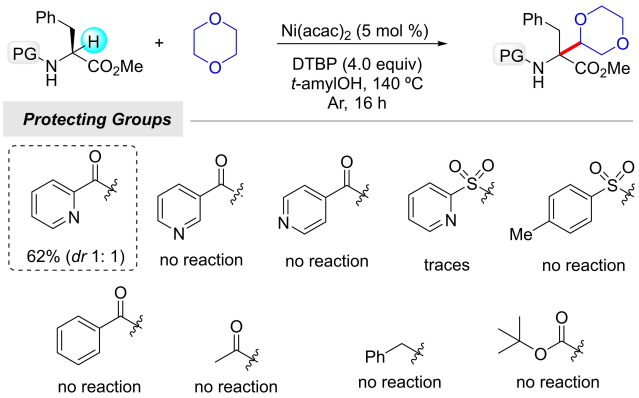
Scheme 1. Radical C–H alkylation of amino acid derivatives.

these results and as part of our interest in the modification of peptides upon radical chemistry,[13] we wondered whether we could use a picolinamide unit as efficient auxiliary to assist the radical alkylation of trisubstituted amino acid compounds with solvent-like molecules, thereby complementing existing methodologies and broadening the scope for assembling non-proteinogenic tetrasubstituted compounds. While this work was in progress, strategically designed α-amino acid Schiff bases have been used by Yazaki and Ohshima to forge highly congested amino acid derivatives.[14] In this communication, we report a reliable and scalable C–H alkylation manifold featuring the use of ethers and cycloalkanes toward the assembly of unnatural amino acid derivatives including short peptides. Remarkably, the required picolinamide moiety can be easily cleaved to deliver the corresponding amino group, hence outcompeting with the use of *N*-aryl units in these endeavors.

To evaluate the feasibility of our alkylation platform, we selected the coupling of phenylalanine **1 a** (PA-Phe-OMe) and cheap and commercially available 1,4-dioxane (Table 1). Careful evaluation of the reaction parameters revealed the viability of our approach to install the corresponding ether at the α-amino acid backbone in a radical fashion. The latter may likely happen through a dual activation of both substrates and the intermediacy of a carbon centered radical in the adjacent position to the oxygen atom of 1,4-dioxane.[1] In accordance with studies by You,[12] $Ni(acac)_2$ showed superior activity to that of other metal sources (entries 1–4). Likewise, di-*tert*-butyl peroxide (DTBP) afforded better results than other related peroxides (entries 5–6). The addition of *tert*-amyl alcohol as co-solvent was shown beneficial, whereas the use of PhCl led to traces of product **2 aa** (entry 7). Importantly, the amount of $Ni(acac)_2$ could be reduced from 20 mol% to 10 mol% or even 5 mol% at the expense of using DTBP in excess at 140 or 120 °C, respectively (entries 11 and 12). In this regard, a blank experiment in the absence of $Ni(acac)_2$ underpinned its role as a mere additive to favor the reaction conversion and ruled out its role as a catalyst as a remarkable 51% yield was obtained in its absence (entry 13). The performance of the process under argon was found crucial as the use of an oxygen atmosphere resulted in traces of **2 aa** (entry 14).

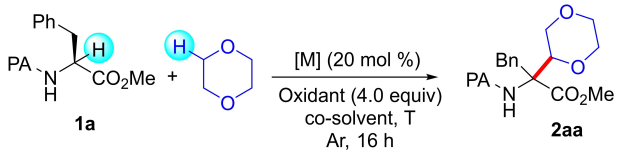
Intrigued by the successful use of 2-pyridinecarbonyl as efficient auxiliary, the influence of other *N*-protecting groups was subsequently evaluated (Scheme 2). To our surprise, neither the use of 3-pyridinecarbonyl, 4-pyridinecarbonyl, nor 2-pyridinesulfonyl groups was viable for assisting the targeted alkylation, thus excluding electronic factors as the dominant ones in the stabilization of the transient radical intermediates. Likewise, other groups devoid of the coordinating nitrogen atom such as tosyl, benzoyl, acetyl, benzyl or Boc groups ushered in the entire lack of reactivity and the starting materials remained intact under the standard reaction conditions. Accordingly, the easily installed 2-pyridine carbonyl group derived from inexpensive picolinic acid may not act as an innocent protecting group and seemed key to perform the radical alkylation with 1,4-dioxane.

With the optimized conditions in hand, we next investigated the scope of the C(sp^3)–H alkylation protocol with other solvent-like ethers. As depicted on Table 2, not only 1,4-dioxane but also tetrahydrofuran could be used to produce α-alkylated product **2 ab** in good yields. Remarkably, acyclic ethers such as 1,2-dimethoxyethane, dibutyl ether, *tert*-amyl ether, diethyl



Scheme 2. Influence of the *N*-protecting group.

Table 1. C–H alkylation of **1a** with 1,4-dioxane.[a]



entry	[M]	Oxidant	Co-solvent	T (°C)	**2aa** (%)[b]
1	$Co(OAc)_2$	DTBP	none	140	traces
2	$Cu(OAc)_2$	DTBP	none	140	0
3	$FeCl_2$	DTBP	none	140	0
4	$Ni(acac)_2$	DTBP	none	140	50 (1:1)[c]
5	$Ni(acac)_2$	TBPB	none	140	0
6	$Ni(acac)_2$	TBHP	none	140	0
7	$Ni(acac)_2$	DTBP	PhCl	140	traces
8	$Ni(acac)_2$	DTBP	MeCN	140	48 (1:1)[c]
9	$Ni(acac)_2$	DTBP	*t*-amylOH	140	50 (1:1)[c]
10[d]	$Ni(acac)_2$	DTBP	*t*-amylOH	120	54 (1:1)[c]
11[e,f]	**$Ni(acac)_2$**	**DTBP**	***t*-amylOH**	**120**	**61 (1:1)[c]**
12[g]	**$Ni(acac)_2$**	**DTBP**	***t*-amylOH**	**140**	**62 (1:1)[c]**
13	none	DTBP	*t*-amylOH	140	51 (1:1)[c]
14[h]	$Ni(acac)_2$	DTBP	*t*-amylOH	140	0

[a] Reaction conditions: **1a** (0.25 mmol), 1,4-dioxane (1.0 mL), metal salt (20 mol%), oxidant (4.0 equiv.), co-solvent (0.5 mL) at 120–140 °C for 16 h under Ar.
[b] Yield of isolated product after column chromatography.
[c] Diastomeric ratio.
[d] DTBP (6.0 equiv.).
[e] $Ni(acac)_2$ (5 mol%).
[f] DTBP (8.0 equiv.)
[g] $Ni(acac)_2$ (10 mol%).
[h] under O_2 (1 atm). $TBHP_{dec}$ = (*tert*-butyl hydroperoxide solution in decane, 5.0–6.0 M); DCP = dicumyl peroxide; DTBP = di-*tert*-butylperoxide; TBPB = *tert*-butyl peroxybenzoate.

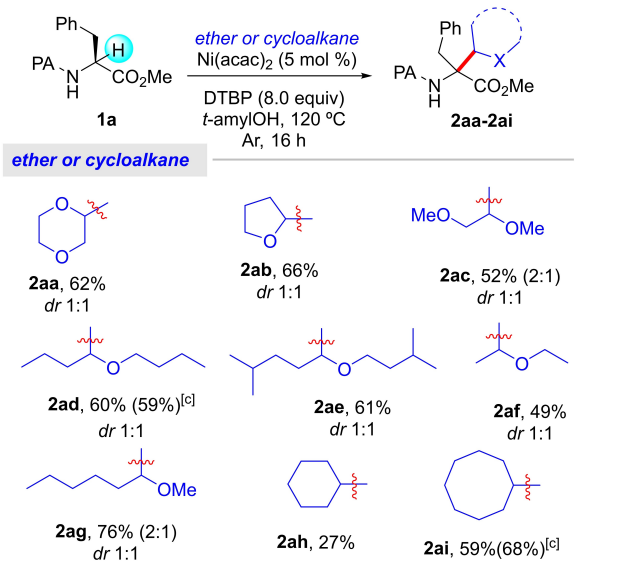
ether and hexyl methyl ether smoothly underwent the corresponding alkylation reaction to deliver products **2ac**–**2ag** in up to 76% yield. When using ethers including a methoxy group a mixture of isomers was detected by ^{1}H NMR analysis with predominant formation of the product arising from the methylene activation versus the one from the methyl ether unit (2:1 ratio in **2ac** and **2ag**). In all cases, the products were obtained as mixtures of diastereomers (*dr* 1:1).

Importantly, the functionalization of inert hydrocarbon C(sp^3)–H bonds could be achieved and unactivated cyclohexane and cyclooctane were also employed to produce the corresponding alkylated compounds **2ah** and **2ai** in 27% and 59% yields, respectively.[15] Accordingly, a variety of commonly used organic solvents played a dual role of reactant and solvent, thereby resulting in the formation of sterically hindered C(sp^3)–C(sp^3) linkages. Unfortunately, the use of trisubstituted ethers or hydrocarbons resulted in no reaction, which may be due to sterical issues.[16] Noteworthy, the robustness and practical value of the method was demonstrated by performing the coupling of **1a** with dibutyl ether and cyclooctane in a gram-scale.

With the aim to evaluate the generality of this alkylation manifold, we next tackled the synthetic scope concerning the amino acid residue (Table 3). Various picolinamides derived from a number of amino acid residues could be coupled with dibutyl ether and cyclooctane in moderate to good yields (up to 82% yield). The backbone of Glu, Ser, Asp, Tyr, Met, Leu, Ala, Gly and β-Ala could be efficiently altered to produce the corresponding α-alkylated products **2b**–**2l**. More sterically encumbered residues such as proline and isoleucine were found incompatible with our radical alkylation. Remarkably, despite the use of an excess of DTBP, oxidizable moieties such as thioether and hydroxyl in Met and Ser, respectively, remained unaffected. The tolerance of an aryl chloride in **2g** provides ample room for further derivatizations upon conventional cross-coupling methods. Importantly, the scalability of the process was illustrated by the gram-scale synthesis of compounds **2ka** and **2kb**.

We next explored the synthetic scope in a challenging peptide template. After a careful screening of the reaction conditions (see Table S1),[16] we observed that the alkylation of a set of dipeptides **3a**–**e** with cyclooctane could occur in a metal-free fashion featuring

Table 2. C–H alkylation of **1a** with ethers and alkanes.[a,b]



[a] Reaction conditions: **1a** (0.25 mmol), ether or cycloalkane (1 mL), $Ni(acac)_2$ (5 mol%), DTBP (8.0 equiv.) in *t*-amylOH (0.5 mL) at 120 °C for 16 h under Ar.

[b] Yield of isolated product after column chromatography, average of at least two independent runs.

[c] Reaction conditions: **1a** (3.52 mmol, 1.0 g), cyclooctane or Bu_2O (14 mL), $Ni(acac)_2$ (10 mol%), DTBP (4.0 equiv.) in *t*-amylOH (7 mL) at 140 °C for 16 h under Ar.

the use dicumyl peroxide as oxidant. In these cases, the addition of $Ni(acac)_2$ did not improve the reaction yields and hence an appealing metal-free procedure was followed. As shown in Table 4, the Gly unit within peptides bearing Phe, Leu, Glu and Pro could be modified to produce sterically encumbered architectures **4a**–**4d**. Notably, a more complex tetrapeptide could be also alkylated with cyclooctane, albeit product **4e** was obtained in 44% yield. Unfortunately, attempts with PA-Phe-Phe-OMe and PA-Phe-Pro-OMe were unsuccessful, which could be attributed to a high sterical hindrance.

Although the introduction of a picolinamide unit is required for the process to occur, the latter can be easily removed under treatment with HCl and Zn.[17] As depicted on Scheme 3, deprotection of **2ai** afforded α,α-disubstituted compound **5a** housing a versatile free-amino group in excellent yields. The deprotection step can be also performed in a sequential mode without isolating the ensuing alkylated compound to deliver **5a** in 60% overall yield. Notably, the cleavage of the picolinamide unit within dipeptide **4b** can be achieved via a two-step one-pot operation to deliver Boc-protected product **5b** in 67% yield.

Concerning the reaction mechanism, it is extensively accepted that DTBP can readily form alkyl radicals from hydrocarbons and ethers[1] and, in fact, we observed that the reaction was entirely suppressed in the presence of radical traps such as TEMPO, BHT and 1,1-diphenylethylene. However, the actual nature of the electrophilic intermediate derived from the amino acid counterpart in these oxidative couplings still remains a matter of debate. In this respect, elemental steps to produce *N*-centered or carbon radicals as well as transient radical cations may be likely involved under these experimental conditions.[18] The latter may undergo a radical-radical coupling or could also evolve to the formation of other electrophilic species such as a neutral imine or an iminium ion.[11] Accordingly, computational studies would be clearly required to propose a reliable mechanistic pathway.

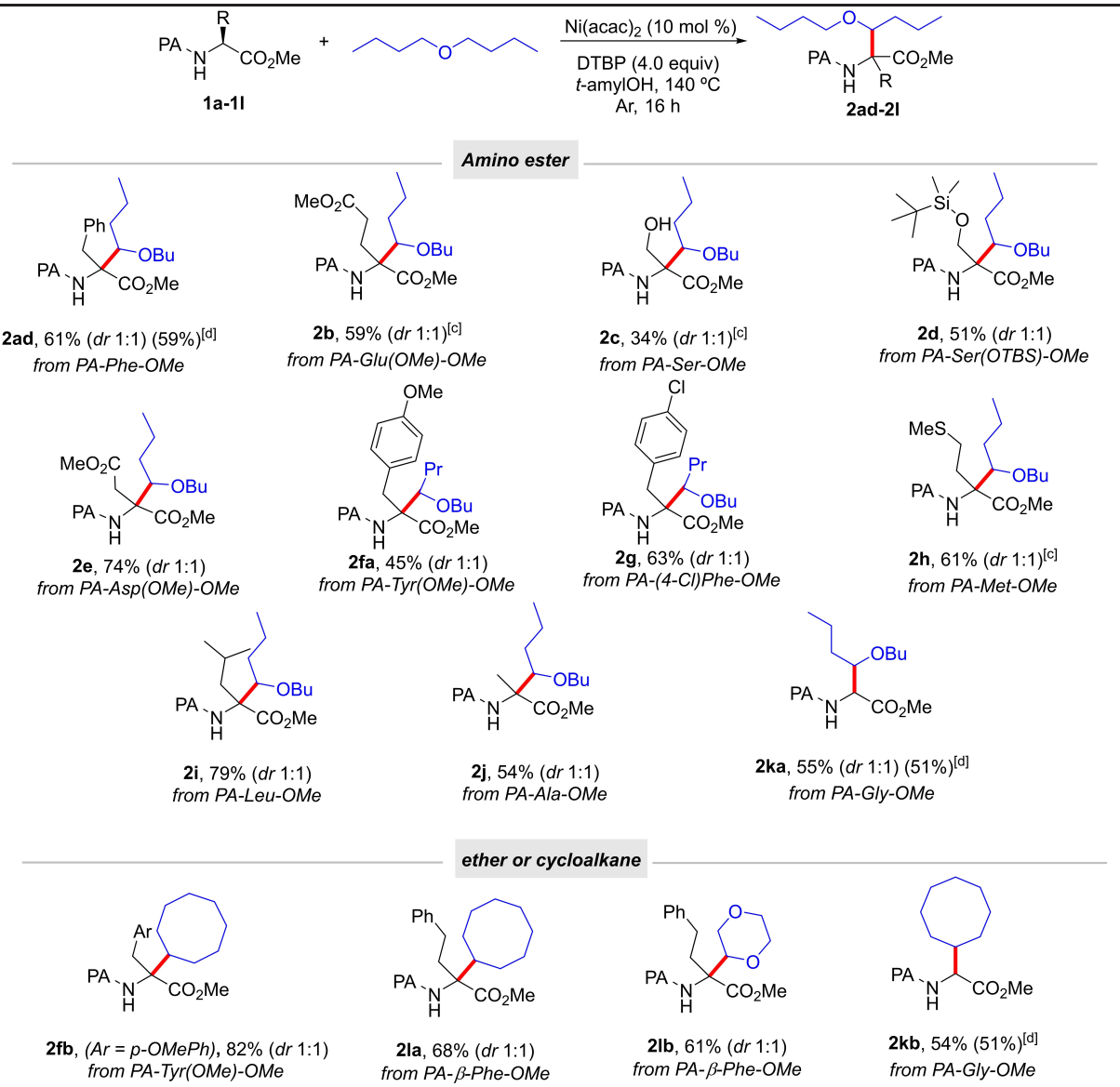
In summary, we have unlocked the chemical versatility of ethers and unactivated cycloalkanes as sustainable feedstock to assemble sterically encumbered tetrasubstituted amino acid compounds. Salient features of this method are the widespread availability and low-cost of the solvent-like counterparts, scalability and the easy installation and cleavage of the required 2-pyridinecarbonyl group. As a result, this dehydrogenative radical coupling represents a useful tool for the modification of biomass compounds and forge sterically hindered new C(sp^3)–C(sp^3) bonds.

Experimental Section

General procedure for the α-alkylation of amino acid derivatives: A reaction tube containing a stirring bar was charged with **1a** (0.25 mmol, 71 mg) and $Ni(acac)_2$ (10 mol%, 6.42 mg). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, 1,4-dioxane (1.0 mL), a commercially available solution of DTBP (1.0 mmol, 182 µL) and *t*-amylOH (0.5 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to 140 °C in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford 58 mg (62% yield) (*dr* 1:1) of **2aa** as a colorless oil. The characterization data correspond to a diasteromeric mixture (*dr* 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 0.5H), 8.75 (s, 0.5H), 8.58–8.50 (m, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.86 (tdd, J = 7.7, 1.7, 0.6 Hz, 1H), 7.47–7.38 (m, 1H), 7.23–7.16 (m, 2H), 7.15–7.06 (m, 3H), 4.32–4.13 (m, 2H), 4.10–4.02 (m, 1H), 3.83 (s, 1.5H), 3.81 (s, 1.5H), 3.78–3.63 (m, 3H), 3.61–3.51 (m, 2H), 3.49–3.34 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 170.5, 164.1, 164.0, 149.9, 149.8, 148.44, 148.42, 137.43, 137.41, 135.8, 135.2, 130.2, 130.1, 128.4, 128.3, 127.3, 127.0, 126.4, 122.1, 122.0, 78.9, 75.9, 68.2, 67.9, 67.7, 66.6, 66.5, 66.4, 65.7, 53.0, 52.7, 37.7, 35.3. IR (cm^{-1}): 3358, 2955, 2917, 2855, 1742, 1676, 1514, 1434, 1114, 1089, 731, 701. HRMS (ESI) m/z: (M^+) *calcd.* for ($C_{20}H_{22}N_2O_5$): 370.1529, *found* 370.1528.

General procedure for the α-alkylation of peptides: A reaction tube containing a stirring bar was charged with peptide derivative **3a** (0.25 mmol, 85 mg) and dicumyl peroxide

Table 3. Assembly of tetrasubstituted amino ester compounds upon C–H alkylation with ethers.[a,b]



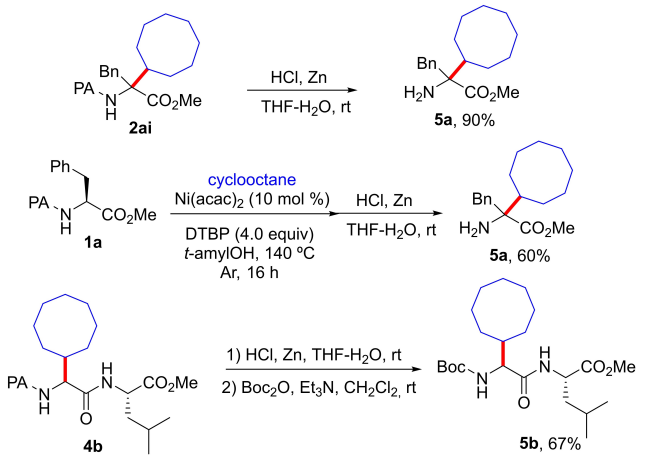
[a] Reaction conditions: **1** (0.25 mmol), ether or cycloalkane (1 mL), $Ni(acac)_2$ (10 mol%), DTBP (4.0 equiv.) in *t*-amylOH (0.5 mL) at 140 °C for 16 h under Ar.

[b] Yield of isolated product after column chromatography, average of at least two independent runs with a variable yield by no more than 5% between runs.

[c] **1** (0.25 mmol), ether or cycloalkane (1 mL), $Ni(acac)_2$ (5 mol%), DTBP (8.0 equiv.) in *t*-amylOH (0.5 mL) at 120 °C for 16 h under Ar.

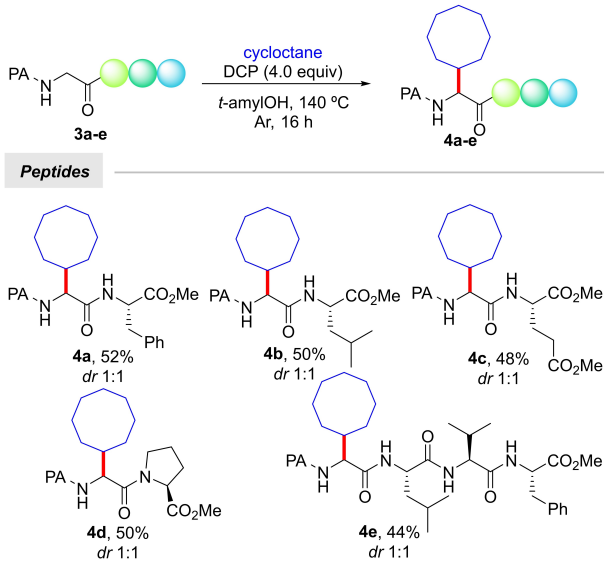
[d] Reaction performed at gram-scale.

(1.0 mmol, 270 mg). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, cyclooctane (1.0 mL), and *t*-amylOH (0.50 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to 140 °C in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford 58.7 mg (52% yield) of **4a** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, J = 4.8, 1.5 Hz, 1H), 8.42 (d, J = 9.3 Hz, 1H), 8.17 (dd, J = 7.9, 1.2 Hz, 1H), 7.86 (td, J = 7.7, 1.7 Hz, 1H), 7.45 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 7.20–6.92 (m, 5H), 6.56 (d, J = 7.9 Hz, 1H), 4.88 (dd, J = 7.8, 6.1 Hz, 1H), 4.45 (dd, J = 9.3, 6.7 Hz, 1H), 3.70 (s, 3H), 3.16 (dd, J = 13.9, 5.7 Hz, 1H), 3.06 (dd, J = 13.9, 6.5 Hz, 1H), 2.28–2.22 (m, 1H), 1.76–1.13 (m, 14H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 170.9, 164.6, 149.4, 148.4, 137.4, 135.8, 129.3, 128.6, 127.1, 126.5, 122.5, 59.1, 53.2, 52.4, 39.2, 38.0, 30.4, 28.1, 26.8, 26.5, 26.4, 26.1, 25.4. IR (cm^{-1}): 3303, 2920, 1741, 1655, 1510,



Scheme 3. Removal of the picolinamide group.

Table 4. C–H alkylation of peptides.[a,b]



[a] Reaction conditions: **3** (0.25 mmol), cyclooctane (1 mL), DCP (4.0 equiv.) in *t*-amylOH (0.5 mL) at 140 °C for 16 h under Ar.

[b] Yield of isolated product after column chromatography, average of at least two independent runs.

1177. HRMS (ESI) m/z: (M^+) *calcd.* for ($C_{26}H_{33}N_3O_4$): 451.2471, *found* 451.2460.

Acknowledgements

We are grateful to Ministerio de Ciencia e Innovación (RTI2018-093721-B-I00, MCI/AEI/FEDER, UE) and Basque Government (IT1033-16) for financial support. We thank for technical and human support provided by Central Service of Analysis-SGIker of UPV/EHU and European funding (ERDF and ESF).

References

[1] a) Y. Feng, X. Ye, D. Huang, S.-R. Guo, *Synthesis* **2022**, *54*, 315; b) A. Batra, P. Singh, K. N. Singh, *Eur. J. Org. Chem.* **2017**, 3739; c) S.-R. GUO, P. S. KUMAR, M. YANG, *Adv. Synth. Catal.* **2017**, *359*, 2; d) M. K. Lakshman, P. K. Vuram, *Chem. Sci.* **2017**, *8*, 5845; e) S.-Y. Zhang, F.-M. Zhang, Y.-Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937.

[2] M. D. Delost, D. T. Smith, B. J. Anderson, J. T. Njardarson, *J. Med. Chem.* **2018**, *61*, 10996.

[3] a) J. Li, C.-H. Huang, C.-J. Li, *Trends Chem.* **2022**, *4*, 479; b) Y. Liao, F. Liu, Z.-J. Shi, *Chem. Commun.* **2021**, *57*, 13288; c) B. Liu, A. M. Romine, C. Z. Rubel, K. M. Engle, B.-F. Shi, *Chem. Rev.* **2021**, *121*, 14957; d) Z. Chen, M.-Y. Rong, J. Nie, X.-F. Zhu, B.-F. Shi, J.-A. Ma, *Chem. Soc. Rev.* **2019**, *48*, 4921; e) A. Banerjee, S. Sarkar, B. K. Patel, *Org. Biomol. Chem.* **2017**, *15*, 505; f) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi, A. Lei, *Chem. Rev.* **2015**, *115*, 12138.

[4] a) F. J. A. Troyano, K. Merkens, K. Anwar, A. Gómez-Suárez, *Angew. Chem. Int. Ed.* **2021**, *60*, 1098; *Angew. Chem.* **2021**, *133*, 1112; b) M. S. Kang, T. W. S. Kong, J. Y. X. Khoo, T.-P. Loh, *Chem. Sci.* **2021**, *12*, 13613; c) J. N. deGruyter, L. R. Malins, P. S. Baran, *Biochemistry* **2017**, *56*, 3863; d) A. F. M. Noisier, M. A. Brimble, *Chem. Rev.* **2014**, *114*, 8775.

[5] M. San Segundo, A. Correa, *Synthesis* **2018**, *50*, 2853.

[6] a) S. Sen, J. Das, D. Maiti, *Tetrahedron Chem.* **2022**, *1*, 100005; b) B.-B. Zhan, M.-X. Jiang, B.-F. Shi, *Chem. Commun.* **2020**, *56*, 13950; c) H.-R. Tong, B. Li, G. Li, G. He, G. Chen, *CCS Chem.* **2020**, *2*, 1797; d) W. Wang, M. Lorion, J. Shah, A. R. Kapdi, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 14700; *Angew. Chem.* **2018**, *130*, 14912.

[7] L. Zhao, C.-J. Li, *Angew. Chem. Int. Ed.* **2008**, *47*, 7075; *Angew. Chem.* **2008**, *120*, 7183.

[8] a) T. Tian, Z. Li, C.-J. Li, *Green Chem.* **2021**, *23*, 6789; b) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74; *Angew. Chem.* **2014**, *126*, 76.

[9] W.-T. Wei, R.-J. Song, J.-H. Li, *Adv. Synth. Catal.* **2014**, *356*, 1703.

[10] a) M. San Segundo, A. Correa, *ChemSusChem* **2018**, *11*, 3893; b) M. San Segundo, I. Guerrero, A. Correa, *Org. Lett.* **2017**, *19*, 5288.

[11] a) P. Andrade-Sampedro, A. Correa, J. M. Matxain, *J. Org. Chem.* **2020**, *85*, 13133; b) A. S.-K. Tsang, A. S. K. Hashmi, P. Comba, M. Kerscher, B. Chan, M. H. Todd, *Chem. Eur. J.* **2017**, *23*, 9313.

[12] a) M. Tan, K. Li, J. Yin, J. You, *Chem. Commun.* **2018**, *54*, 1221; b) H. Yu, Z. Liu, J. Lin, *Synlett* **2016**, *27*, 1711; c) K. Li, Q. Wu, J. Lan, J. You, *Nat. Commun.* **2015**, *6*, 8404; d) K. Li, G. Tan, J. Huang, F. Song, J. You, *Angew. Chem. Int. Ed.* **2013**, *52*, 12942; *Angew. Chem.* **2013**, *125*, 13180.

[13] a) I. Urruzuno, P. Andrade-Sampedro, A. Correa, *Org. Lett.* **2021**, *23*, 7279; b) M. San Segundo, A. Correa, *Chem. Sci.* **2020**, *11*, 11531; c) I. Guerrero, A. Correa,

Org. Lett. **2020**, *22*, 1754; d) M. San Segundo, A. Correa, *Chem. Sci.* **2019**, *10*, 8872.
[14] T. Tsuji, K. Hashiguchi, M. Yoshida, T. Ikeda, Y. Koga, Y. Honda, T. Tanaka, S. Re, K. Mizuguchi, D. Takahashi, R. Yazaki, T. Ohshima, *Nat. Synth.* **2022**, *1*, 304.
[15] For the alkylation of terminal *N*-aryl glycines with alkanes, see: H. Peng, J.-T. Yu, Y. Jiang, H. Yang, J. Cheng, *J. Org. Chem.* **2014**, *79*, 9847.
[16] For further details, see the *Supporting Information*.
[17] For example, see: a) B. Han, B. L. Qi, P. Yang, G. He, G. Chen, *Org. Lett.* **2020**, *22*, 6879; b) B. Li, X. Li, B. Han, Z. Chen, X. Zhang, G. He, G. Chen, *J. Am. Chem. Soc.* **2019**, *141*, 9401; c) D. H. O' Donovan, C. De Fusco, D. R. Spring, *Tetrahedron Lett.* **2016**, *57*, 2962.
[18] a) F. Babawale, K. Murugesa, R. Narobe, B. König, *Org. Lett.* **2022**, *24*, 4793; b) Y. Song, H. Zhang, J. Guo, Y. Shao, Y. Ding, L. Zhu, X. Yao, *Eur. J. Org. Chem.* **2021**, *2021*, 5914; c) L. Yang, Z. Qiu, J. Wu, J. Zhao, T. Shen, X. Huang, Z.-Q. Liu, *Org. Lett.* **2021**, *23*, 3207; d) L. Yang, Z. Qiu, J. Wu, J. Zhao, T. Shen, X. Huang, Z.-Q. Liu, *Angew. Chem. Int. Ed.* **2018**, *57*, 15841; *Angew. Chem.* **2018**, *130*, 16067.