

Deaminative and Decarboxylative Catalytic Alkylation of Amino Acids with Ketones**

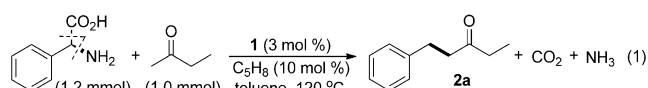
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As one of the most important building blocks of living organisms, α -amino acids constitute a highly attractive class of bio-based reagents for the synthesis of complex organic compounds.^[1–4] Since amino acids are readily available from biomass feedstock, using them as reagents would be highly meritable from the viewpoint of replacing petrochemical-based reagents and for designing renewable and sustainable synthetic methods. While amino acids have been successfully employed as the chiral scaffolds for metal catalysts^[5–7] and as organocatalysts,^[8,9] they have not been widely utilized as reagents in organic synthesis, in part because an efficient catalytic C–N bond cleavage method for amino acids is not available for associated C–C coupling reactions. In this regard, nature provides ample inspiration for effective design on C–N bond-cleavage methods for amines and related nitrogen compounds.^[10–15] Natural metalloenzymes such as CYP450 and methane monooxygenases have been found to mediate selective oxidative dealkylation of amines.^[10,11] In biochemical catabolic pathways, deamination of α -amino acids is efficiently catalyzed by deaminase, oxidase, and dehydrogenase enzymes.^[12] N-Demethylation of both DNA and mRNA has also been shown to be intricately involved in gene regulating processes.^[13–15]

Designing catalytic C–N bond-cleavage methods for amines and related nitrogen compounds poses a challenging problem in the field of homogeneous catalysis because of a relatively strong C–N bond strength and their tendency for undergoing kinetically favored dehydrogenation and other side reactions, as well as the potential for catalyst poisoning. As a result, only a few catalytic C–N bond cleavage methods have been developed over the years, and the most notable examples include: the deaminative coupling of arylamines,^[16] arene–alkyne coupling of arylamides,^[17] and dealkylation and deallylation reactions of amines.^[18–21] A broadly applicable catalytic C–N bond-cleavage method is essential not only for efficient utilization of bio-derived nitrogen compounds in organic synthesis, but also for designing cost-effective and environmentally sustainable synthesis and reforming process for biomass nitrogen feedstock.^[22]

Inspired by nature's ability to promote selective deamination processes, we have been searching for novel catalytic

C–N cleavage methods for amino compounds. Our idea stems from the recent discovery that a well-defined cationic ruthenium hydride complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ (**1**) is a selective catalyst for the dehydrative C–H alkylation reactions of alcohols.^[23,24] Since the alkylation reaction is driven by the formation of water, we surmized that the analogous deaminative coupling reaction might be achievable from using amino substrates. Herein, we disclose a highly selective catalytic deaminative and decarboxylative coupling reaction of amino acids with ketones. The catalytic coupling method achieves direct C–C and C–N bond cleavage of amino acid substrates, and exhibits high chemo- and regioselectivity in forming the α -alkylated ketone products without using any reactive reagents or protecting groups.



To assess the feasibility of the deaminative coupling reaction, we initially screened a number of ruthenium catalysts for the coupling reaction of (*S*)-phenylglycine with butanone under the reaction conditions stipulated in Equation (1). Among screened catalysts, the catalyst **1** shows distinctively high activity in forming the coupling product 1-phenyl-3-pentanone (**2a**; see Table S1 in the Supporting Information). Moreover, the catalyst mediates highly regioselective alkylation to the sterically less demanding α -ketone carbon atom in forming the product **2a**. Following the previously developed protocol for generating an active ruthenium vinyl species,^[25] we have been able to promote the catalytic activity of **1** by adding a substoichiometric amount of an alkene (10 mol %). We have also been able to trap both ammonia and carbon dioxide byproducts by chemically converting them into isolable forms. Thus, carbon dioxide is readily converted into $BaCO_3$ (82 % CO_2), while the treatment of the crude reaction mixture with $HCl(aq)$ is used to estimate the formation of ammonia (79 % NH_3) by following a literature procedure.^[26,27]

We surveyed the substrate scope of the coupling reaction by using **1** (Table 1). In general, α -amino acids with both aliphatic and aryl side chains readily react with ketones to form the α -alkylated ketone products **2**. The coupling of (*S*)-phenylglycine with both 2- and 3-methylcyclohexanone result in a highly diastereoselective formation of the α -alkylated products **2i** and **2j**, respectively (entries 9 and 10). A number of oxygen and nitrogen groups are tolerated in the coupling with aryl-substituted ketone substrates (entries 11–17). The coupling of an amino acid having a chiral substituent, L-

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Table 1: Deaminative and decarboxylative coupling of α -amino acids with ketones.^[a]

Entry	Amino acid	Ketone	Product(s)	<i>t</i> [h]	Yield [%] ^[b]
1				12	90
2		R = Et	2b	12	88
3				12	79
4		X = H, R = H	2c	12	90
5		X = OMe, R = H	2d	8	80
6		X = OMe, R = Me	2e	8	76
7		X = H, R = Ph	2f		
8				8	95
9				8	89
10		R = Me, R' = H	($\pm$)- 2i (> 20:1 d.r.)	12	83
11		R = H, R' = Me	($\pm$)- 2j (> 20:1 d.r.)	12	85
12				12	90
13		X = OMe, R = H	2k	12	80
14		X = OMe, R = Me	2l	12	74
15		X = H, R = H	2m	12	80
16		X = Cl, R = H	2n	12	74
17		X = CN, R = H	2o	12	90
18		X = NH2, R = H	2p	12	92
19		X = NC4H8O, R = H	2q	12	92
20				8	90
21		X = OMe, <i>n</i> = 1	2s	8	92
22		X = H, <i>n</i> = 2	2t	8	89
23				12	93
24				8	88
25		X = H, R = Me	2v	12	90
26		X = H, R = <i>i</i> Pr	2w	12	75
27		X = OMe, R = Bn	2x	12	80
28		X = OMe	2y	10	75
29		R = CH2OBn	2z	12	95
30		X = H	2aa		
31		R = CH2CH2CO2Me			
32		X = H, R = CH2Cy			

[a] Reaction conditions: amino acid (1.2 mmol), ketone (1.0 mmol), cyclopentene (0.1 mmol), toluene (2 mL), **1** (3 mol %), 110–120 °C. [b] Yield of isolated product is based on the ketone substrate. The d.r. values were determined by ¹H NMR spectroscopy.

isoleucine, with 4-methoxyacetophenone directly forms an optically active product (+)-**2u** (entry 21). Protected α -amino acids having oxygenated side chains such as L-serine and L-aspartic acid derivatives smoothly afford the coupling products **2y** and **2z**, respectively (entries 25 and 26). In most cases, racemic D,L-amino acids can be used without any significant change in the product yields, but a secondary amino acid, L-proline, does not yield any coupling products. We also compared the analogous coupling of aliphatic and benzylic amines with ketones, and in these cases, similar alkylation products are formed but with considerably lower yield because of the formation of imine and other side products resulting from the homocoupling of amines. To the best of our knowledge, the catalytic method represents a unique set of examples on using bio-based amino acids as the alkylating agent for the C–C coupling reaction.

In an effort to extend its synthetic utility, we next inspected the coupling reaction of β -amino acids with ketones (Table 2). In the coupling of (*S*)-3-amino-2-methylpropanoic acid with aryl-substituted ketones, the *n*-propyl group is regioselectively alkylated to form the coupling products **3a–f** (entries 1–6). The coupling reaction with 2-phenylcyclohexanone leads to the diastereoselective formation of **3g** (entry 7). In contrast, a modestly diastereoselective formation of the ethylated product **3h** is observed from the coupling of 3-aminopropanoic acid with 2-phenylcyclohexanone (entry 9). Generally, the coupling reaction with branched β -amino acids is quite sluggish, thus leading to the decomposition products predominantly. Despite such difficulties, we have been able to effect the coupling reaction of the branched β -amino acids such as 3-aminobutanoic acid and 3-amino-3-phenylpropanoic acid with acetophenone and indanone substrates to form the alkylated products **3i–k** (entries 10–12).

To further demonstrate synthetic versatility of the catalytic coupling method, we employed a number of bioactive ketone substrates to probe chemo- and stereoselectivity patterns on the alkylation products (Table 3). The alkylation of cholesterol (which readily undergoes alcohol dehydrogenation under the reaction conditions) and *trans*-androsterone with (*S*)-phenylglycine occurs in a highly regio- and stereoselective manner to give the *anti*-selective alkylation products, (+)-**4a** and (+)-**4b**, respectively. In contrast, the *cis*-fused deoxycholic acid benzyl ester with (*S*)-phenylglycine leads to the *syn*-selective alkylation product (+)-**4c**.

The alkylation of L-isoleucine with indanone leads to a modestly diastereoselective formation of the coupling product **4d** (d.r. = 2:1). The coupling reaction of (*S*)-phenylglycine with dihydro- β -ionone proceeds in a regioselective fashion to give **4e**, while the coupling of L-tryptophan with 4-methoxyacetophenone yields the coupling product **4f**, thus resulting from the dehydrogenation of indole moiety. The regio- and diastereoselective formation of these alkylation products can

Table 2: Deaminative and decarboxylative coupling of β -amino acids with ketones.^[a]

Entry	Amino acid	Ketone	Product(s)	t [h]	Yield [%] ^[b]
1				12	80
2		X = H, R = H	3a	12	85
3		X = OMe, R = H	3b	8	78
4		X = H, R = Me	3c	8	90
		X = H, R = Ph	3d		
5				8	90
6		n = 1	3e	16	83
		n = 2	3f		
7			($\pm$)- 3g (10:1 d.r.)	12	90
8				12	89
9			($\pm$)- 3h (3:2 d.r.)	12	83
10		X = OMe	3i	12	81
11		X = H	3j	12	78
12				12	80

[a] Reaction conditions: amino acid (1.2 mmol), ketone (1.0 mmol), cyclopentene (0.1 mmol), toluene (2 mL), **1** (3 mol %), 110–120 °C.

[b] Yield of isolated product is based on the ketone substrate. The d.r. values were determined by ¹H NMR spectroscopy.

readily be explained from imposing a sterically least hindered ruthenium enolate species.

We performed the following experiments to gain mechanistic insights into the coupling reaction. First, the treatment of C₆D₅COCD₃ with L-leucine leads to substantial deuterium incorporation at both α - and β -carbon atoms on the coupling product [D]-**2m** [Eq. (2)]. The observed hydrogen–deuterium exchange pattern is consistent with a facile keto–enol tautomerization of the ketone substrate and the *ortho*-arene

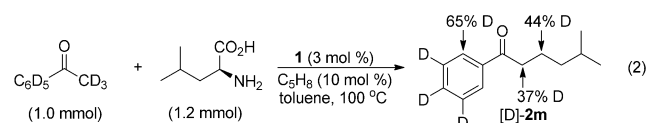
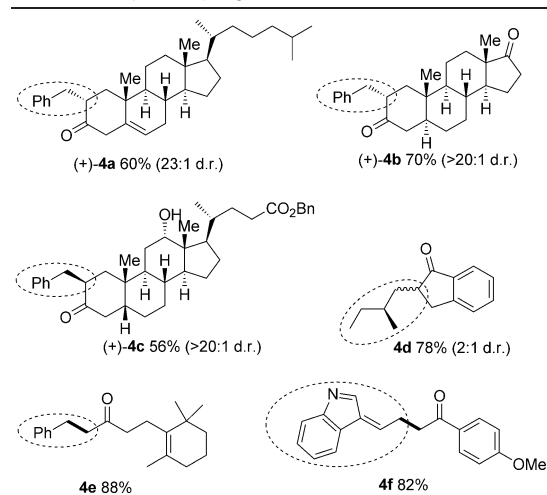
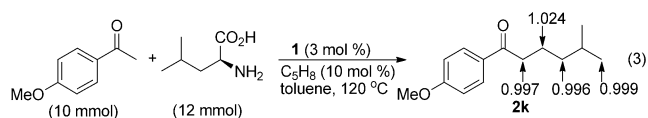


Table 3: Catalytic coupling of α -amino acids with bioactive ketones.^[a]



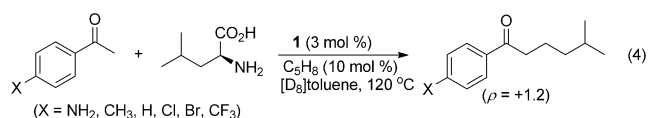
[a] Reaction conditions: amino acid (1.2 mmol), ketone (1.0 mmol), cyclopentene (0.1 mmol), toluene (2 mL), **1** (3 mol %), 110–120 °C. Yields are those for the isolated product. The d.r. values were determined by ¹H NMR spectroscopy.

C–H exchange. The extensive deuterium incorporation on the β -carbon atom can be interpreted as an amine–imine hydrogenation/dehydrogenation of the amino acid substrate under the reaction conditions. Second, the NMR technique reported by Singleton and co-workers is used to measure the ¹²C/¹³C kinetic isotope effect (KIE) from the coupling reaction of 4-methoxyacetophenone with L-leucine [Eq. (3)].^[28] The most pronounced carbon KIE is observed for the β -carbon atom of **2k**, when the ¹²C/¹³C ratio of the product obtained at a low conversion (KIE on C3 = 1.024; average of 3 runs; see Table S2 in the Supporting Information). The unique carbon KIE on the β -carbon atom of **2k** suggests that the C–N bond cleavage is intimately involved in the turnover limiting step of the coupling reaction.

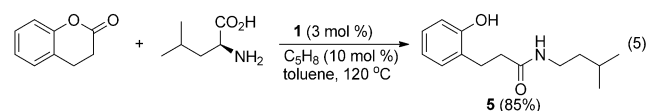


To further probe electronic effect of the ketone substrate, a Hammett plot is constructed from the reaction of a series of *p*-X-C₆H₄COMe (X = NH₂, OCH₃, CH₃, H, Cl, CN) with L-leucine [Eq. (4)]. A linear correlation from the relative rate versus the Hammett σ_p is observed with a positive slope ($\rho = +1.2 \pm 0.2$; see Figure S2 in the Supporting Information). Strong promotional effects by *para*-electron-withdrawing groups suggests a substantial build-up of cationic character on the α -carbon atom of the ketone substrate, and the results can be explained by the formation of a cationic ruthenium enolate species.

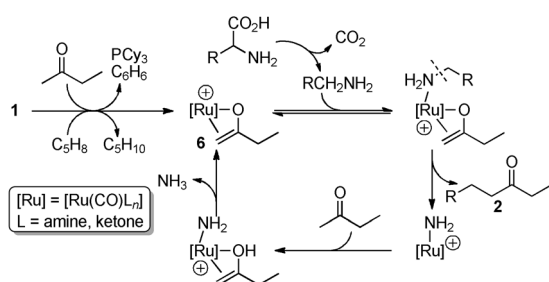
To probe the deamination versus decarboxylation sequence, we surveyed a number of different carbonyl substrates with L-leucine. The trapped amide product **5** is



successfully obtained from the treatment of dihydrocoumarin with L-leucine [Eq. (5)]. The selective formation of the amide product **5** supports a preferential decarboxylation over the deamination step for the amino acid substrate. Transition metal catalyzed decarboxylative coupling methods have been successfully employed for the synthesis of complex organic molecules.^[29]



Although details still remain to be established, we propose a working mechanistic hypothesis for the coupling reaction on the basis of these experimental results (Scheme 1). We propose that the cationic ruthenium(II)



Scheme 1. Plausible mechanistic pathway for the alkylation of α -amino acid with 2-butanone.

enolate species **6**, initially generated from the keto–enol tautomerization and dehydrogenation steps, is the key species for the coupling reaction.^[30,31] The observed deuterium exchange pattern on the coupling product [D]-**2m** is consistent with a facile and reversible enolization of the ketone substrate via the ruthenium enolate species **6**.^[32] Late transition metal/enolate complexes have been well known to mediate a variety of C–C coupling reactions, including Michael-type conjugate addition and nucleophilic addition reactions.^[33,34] We also showed that the ruthenium hydride complex effectively catalyzes the formation of silyl enol ethers from the coupling reaction of ketones and vinylsilanes.^[35] Though the trapping experiment supports for a preferential decarboxylation, we do not have any direct mechanistic evidence for the decarboxylation process at the present time.

After the initial decarboxylation, the resulting amine substrate proceeds to the C–N bond-cleavage step either by a direct oxidative addition/reductive coupling mechanism or by the formation of an imine and the subsequent coupling with the enolate substrate. In either case, the observed carbon

KIE data provides support for the C–N cleavage as the rate-limiting step in leading to the formation of the alkylated product **2**. The regio- and stereoselective formation of the alkylation product can be readily rationalized from the preferential formation of the sterically least demanding ruthenium enolate complex and an intramolecular addition of the alkyl group. Finally, the extrusion of ammonia byproduct provides the driving force for the regeneration of the ruthenium enolate complex **6**.

In summary, we have successfully developed a novel catalytic alkylation method using readily available amino acid substrates as a bio-based alkylation agent. The salient features of the catalytic method are that it achieves direct C–C and C–N bond cleavage of biomass-derived amino acid substrates, exhibits a broad range of substrate scope, as well as high regio- and stereoselectivity, and it does not require any reactive reagents or pre-functionalization of the substrates in forming the α -alkylated ketone products.

Experimental Section

General procedure for the coupling reaction of an amino acid with a ketone: In a glove box, the amino acid (1.2 mmol), ketone (1.0 mmol), cyclopentene (0.1 mmol), and the Ru catalyst **1** (3 mol %) were dissolved in toluene (2 mL) in a 25 mL Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar. The tube was brought out of the glove box, and was stirred in an oil bath set at 120 °C for 6–12 h. The reaction tube was taken out of the oil bath, and cooled to room temperature. After the tube was open to air, the solution was filtered through a short silica gel column by eluting with CH₂Cl₂ (10 mL), and the filtrate was analyzed by GC and GC-MS. Analytically pure product was isolated by a simple column chromatography on silica gel (280–400 mesh, hexanes/EtOAc = 40:1 to 1:1). The products were completely characterized by NMR spectroscopy and GC-MS methods.

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- [1] G. W. Huber, S. Iborra, A. Corma, *Chem. Rev.* **2006**, *106*, 4044–4098.
- [2] J. N. Chheda, G. W. Huber, J. A. Dumesic, *Angew. Chem.* **2007**, *119*, 7298–7318; *Angew. Chem. Int. Ed.* **2007**, *46*, 7164–7183.
- [3] J. Zakzeski, P. C. A. Bruijninx, A. L. Jongerius, B. M. Weckhuysen, *Chem. Rev.* **2010**, *110*, 3552–3599.
- [4] R.-J. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres, J. G. de Vries, *Chem. Rev.* **2013**, *113*, 1499–1597.
- [5] D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450–1460.
- [6] D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315–319.
- [7] X.-F. Cheng, Y. Li, Y.-M. Su, F. Yin, J.-Y. Wang, J. Sheng, H. U. Vora, X.-S. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 1236–1239.
- [8] W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580–591.
- [9] S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.
- [10] D. Lee, S. J. Lippard, *J. Am. Chem. Soc.* **2001**, *123*, 4611–4612.

- [11] B. Chiavarino, R. Cipollini, M. E. Crestoni, S. Fornarini, F. Lanucara, A. Lapi, *J. Am. Chem. Soc.* **2008**, *130*, 3208–3217.
- [12] N. J. Turner, *Chem. Rev.* **2011**, *111*, 4073–4087.
- [13] T. Melcher, S. Maas, A. Herb, R. Sprengel, P. H. Seeburg, M. Higuchi, *Nature* **1996**, *379*, 460–464.
- [14] A. Herbert, J. Alfken, Y.-G. Kim, I. S. Mian, K. Nishikura, A. Rich, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 8421–8426.
- [15] C. Yi, C.-G. Yang, C. He, *Acc. Chem. Res.* **2009**, *42*, 519–529.
- [16] T. Koreeda, T. Kochi, F. Kakiuchi, *J. Am. Chem. Soc.* **2009**, *131*, 7238–7239.
- [17] B.-J. Li, H.-Y. Wang, Q.-L. Zhu, Z.-J. Shi, *Angew. Chem.* **2012**, *124*, 4014–4018; *Angew. Chem. Int. Ed.* **2012**, *51*, 3948–3952.
- [18] E. Balaraman, B. Gnanaprakasam, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **2010**, *132*, 16756–16758.
- [19] X. Zhao, D. Liu, H. Guo, Y. Liu, W. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 19354–19357.
- [20] M.-B. Li, Y. Wang, S.-K. Tian, *Angew. Chem.* **2012**, *124*, 3022–3025; *Angew. Chem. Int. Ed.* **2012**, *51*, 2968–2971.
- [21] H. Huang, X. Ji, W. Wu, L. Huang, H. Jiang, *J. Org. Chem.* **2013**, *78*, 3774–3782.
- [22] R. A. Sánchez-Delgado, *Organometallic Modelling of the Hydrodesulfurization and Hydrodenitrogenation Reactions*, Kluwer Academic, London, **2002**.
- [23] D.-H. Lee, K.-H. Kwon, C. S. Yi, *Science* **2011**, *333*, 1613–1617.
- [24] D.-H. Lee, K.-H. Kwon, C. S. Yi, *J. Am. Chem. Soc.* **2012**, *134*, 7325–7328.
- [25] K.-H. Kwon, D. W. Lee, C. S. Yi, *Organometallics* **2010**, *29*, 5748–5760.
- [26] J. Mendham, R. C. Denney, J. D. Barnes, M. J. K. Thomas, *Vogel's Quantitative Chemical Analysis*, 6th ed., Prentice Hall, New York, **2000**.
- [27] T. Michałowski, A. G. Asuero, S. Wybraniec, *J. Chem. Educ.* **2013**, *90*, 191–197.
- [28] D. E. Frantz, D. A. Singleton, J. P. Snyder, *J. Am. Chem. Soc.* **1997**, *119*, 3383–3384.
- [29] J. D. Weaver, A. Recio III, A. J. Grenning, J. A. Tunge, *Chem. Rev.* **2011**, *111*, 1846–1913.
- [30] S.-I. Murahashi, H. Takaya, *Acc. Chem. Res.* **2000**, *33*, 225–233.
- [31] J. F. Hartwig, R. A. Andersen, R. G. Bergman, *J. Am. Chem. Soc.* **1990**, *112*, 5670–5671.
- [32] We have not been able to detect any ruthenium enolate species when we monitored a C₆D₆ solution of **1** with acetophenone by VT NMR spectroscopy within the temperature range of 20–80 °C.
- [33] F. Dénès, A. Pérez-Luna, F. Chemla, *Chem. Rev.* **2010**, *110*, 2366–2447.
- [34] K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169–196.
- [35] R. Gao, C. S. Yi, *ACS Catal.* **2011**, *1*, 544–547.