Article

Direct Catalytic Chemoselective #-Amination of Acylpyrazoles: A Concise Route to Unnatural #-Amino Acid Derivatives

Keisuke Tokumasu, Ryo Yazaki, and Takashi Ohshima

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.5b11773 • Publication Date (Web): 09 Feb 2016

Direct Catalytic Chemoselective α-Amination of Acylpyrazoles: A Concise Route to Unnatural α-Amino Acid Derivatives

Keisuke Tokumasu, Ryo Yazaki,* and Takashi Ohshima*

Graduate School of Pharmaceutical Sciences, Kyushu University, Maidashi, Higashi-ku, Fukuoka 812-8582 Japan

ABSTRACT: A direct copper-catalyzed highly chemoselective α-amination is described. Acylpyrazole proved to be a highly efficient enolate precursor of a carboxylic acid oxidation state substrate, while pre-activation by a stoichiometric amount of strong base has been used in catalytic α-aminations. The simultaneous activation of both coupling partners, enolization and metal nitrenoid formation, was crucial for obtaining the product and wide functional group compatibility highlighted the mildness of the present catalysis. The bidentate coordination mode was amenable to highly chemoselective activation over ketone and much more acidic nitroalkyl functionality. Deuterium exchange experiments clearly demonstrated that exclusive enolization of acylpyrazole was achieved without the formation of a nitronate. The present catalysis was applied to late-stage α-amination, allowing for concise access to highly versatile α-amino acid derivatives. The product could be transformed into variety of useful building blocks.

Introduction

α-Amino acids are widely used as biologically active molecules and building blocks in synthetic organic chemistry. Peptide-based drugs have attracted increased attention due to their low number of side effects, and replacement of natural α-amino acid residues with unnatural residues improves their pharmacokinetics and bioactivity.[1] Therefore, extensive efforts are focused on developing an efficient synthesis of unnatural α-amino acids.[2] Most of the earlier methodologies, however, rely on carbon-carbon bond formation, as exemplified by the Strecker type reaction[3] and alkylation of glycine derivatives.[4] Alternatively, α-amination of carboxylic acid oxidation state substrates is considered a straightforward method.[5] Especially, a carbon framework construction followed by late-stage α-amination is advantageous for highly complex α-amino acid synthesis.[6] While catalytic α-amination reactions have been investigated for decades, readily enolizable lower oxidation state substrates, such as aldehydes and ketones, are mostly used as carbonyl donors.

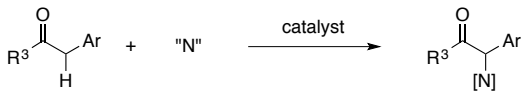
Catalytic deprotonative activation of carboxylic acid oxidation state pronucleophiles and subsequent coupling with electrophiles remains a particularly formidable task due to the intrinsic low acidity of α-protons. Consequently, pre-activation strategies with ketene silyl acetals are generally used. Even when using ketene silyl acetals, however, catalytic α-amination is fairly rare despite a number of precedents of nucleophilic addition to polar electrophiles, such as aldehydes, imines and electron-deficient olefins (Scheme 1-a). Although the pre-activation strategy is highly efficient for synthesizing simple α-amino acids, late-stage α-amination of complex molecules possessing carboxylic acid equivalents has never been applied.[8] Moreover, the use of more than a stoichiometric amount of a strong base limits functional group compatibility, particularly acidic functionalities. Recently, only a few carboxylic acid oxidation state pronucleophiles were applied to catalytic α-aminations (Scheme 1-b). Attachment of an aryl group at the α-position was unavoidable for efficient enolization and a general and complementary catalytic α-amination of carboxylic acid oxidation state pronucleophiles has not been reported. Herein we disclose catalytic α-amination of carboxylic acid oxidation state pronucleophile, allowing for extremely high chemoselectivity and late-stage α-amino acid synthesis through simultaneous activation of both coupling partners (enolization/metal nitrenoid formation) (Scheme 1-c).

Scheme 1. Catalytic α-Amination of Carboxylic Acid Oxidation State Substrates

a) Catalytic α-Amination of Pre-Activated Ketene Silyl Acetals[7a-e]

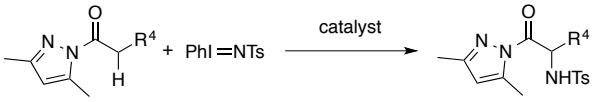
ketene silyl acetals "N" = aminating agent

b) Catalytic α-Amination of α-Aryl Ester Derivatives[7f-h]



acyloxazolidinones, esters "N" = aminating agent

c) Chemoselective and Late-Stage α-Amination of Acylpyrazoles (This work)



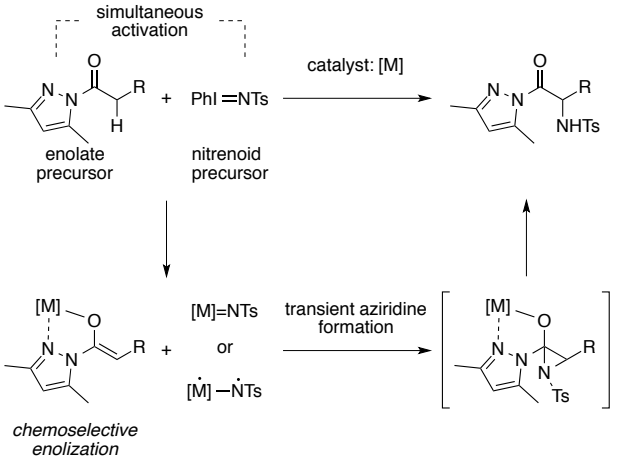
acylpyrazoles ($R^4 \neq Ar$)

- Highly chemoselective
- Late-stage α-aminaiton

Results and discussion

Our strategy for catalytic chemoselective α-amiantion was depicted in Scheme 2. We selected acylpyrazole[9] for chemoselective α-amination as a carboxylic acid oxidation state pronucleophile because 1) acylation of commercially available pyrazole proceeds under mild conditions by conventional methods (acid chloride, condensation reagent, etc.) without requiring a strong base;[10] 2) a weak amide conjugation and bidentate coordination mode enables chemoselective enolization over readily enolizable ketones, allowing for broad functional group compatibility and late-stage α-amination;[11] and 3) acylpyrazole can be easily transformed into diverse functional groups. As an aminating agent, iminoiodinane[12] was selected because iminoiodinane does not generate a nucleophilic coproduct, which would cause an undesired substitution reaction on the carbonyl group of acylpyrazole.[13] Moreover, transition metals generate highly reactive metal nitrenoide species using iminoiodinane, as exemplified by aziridination and C–H amination.[14]

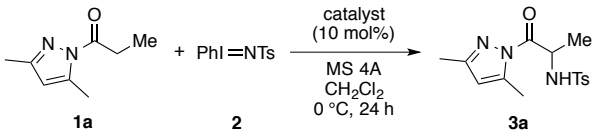
Scheme 2. Simultaneous Activation Strategy for Chemoselective α-Amination



Based on the above strategy, we first evaluated various catalysts in the reaction of acylpyrazole **1a** with iminoiodinane **2** (Table 1). Among them, cationic copper(II) triflate was a competent catalyst for the α-amination reaction (entry 0).[15] This reaction did not require an external base. Less Lewis acidic transition metals were not effective (entries 1 and 2). Lewis acids without an empty *d* orbital for metal nitrenoid formation gave unsatisfactory results (entries 3 and 4). In addition, Brønsted acid catalysts did not give **3a** at all (entries 5 and 6), indicating that highly electrophilic metal nitrenoid formation is crucial for obtaining the product. A variety of copper catalysts were evaluated next. While cationic copper catalysts gave a moderate yield (entries 7-9), less Lewis acidic copper catalysts did not afford **3a** (entries 10-12). Combined use of $CuCl_2$ with AgOTf, which *in situ* generates cationic copper species, increased the catalytic activity (entry 13). These results suggested that proper Lewis acidity is also important to efficiently promote the reaction.

We also evaluated various carboxylic acid oxidation state pronucleophiles (Scheme 3). The substituents on pyrazole were turned out to be crucial for high yield. Acylpyrazole without 3,5-dimethy substituents on pyrazole provided the product in low yield; instead, decomposition of starting material was observed (**4**). In addition, bulker 3,5-diisopropyl substituents almost completely terminated the catalysis, presumably because the coordination to the catalyst was disturbed by bulky substituents (**5**). Other carboxylate donors, acylpyrrole and acylimidazole, which acidity of α-proton would be similar to that of acylpyrazole, were not effective, suggesting that bidentate coordination mode of acylpyrazole was essential (**6** and **7**). Propiophenone did not afford the desired product (**8**). Moreover, bidentate coordinative acyloxazolidione and thiazolidinethione also gave unsatisfactory results (**9** and **10**).

Table 1. Initial Catalyst Screening[a]

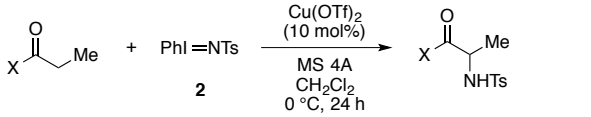


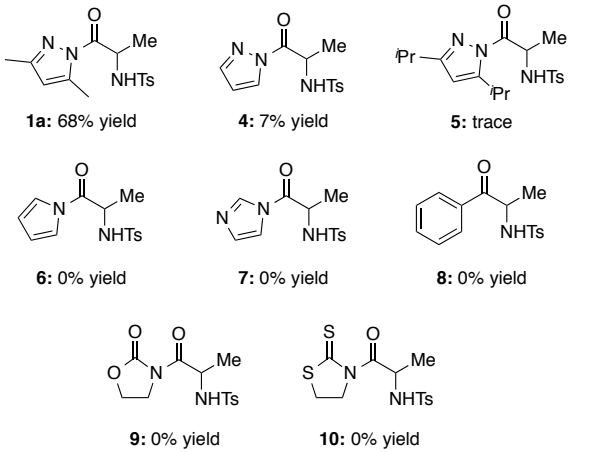
1a **2** **3a**

entry	catalyst	yield (%)	entry	catalyst	yield (%)
0	$Cu(OTf)_2$	68	7[c]	CuOTf	37
1	AgOTf	0	8[d]	$Cu(ClO_4)_2$	43
2[b]	$Rh_2(OAc)_4$	0	9[d]	$Cu(OCOCF_3)_2$	27
3	$Zn(OTf)_2$	0	10	$Cu(OAc)_2$	trace
4	$Sc(OTf)_3$	6	11	$Cu(acac)_2$	trace
5[b]	TfOH	0	12	$CuCl_2$	trace
6[b]	CF_3COOH	0	13[e]	$CuCl_2$ + AgOTf	43

[a]Conditions: **1** (0.4 mmol), **2** (0.2 mmol). Yields were determined by ^{1}H-NMR analysis using 2-methoxynaphthalene as an internal standard. [b]5 mol% catalysts were used. [c]Toluene complex was used. [d]Hydrated metal catalysts were used. [e]10 mol% $CuCl_2$ and 10 mol% AgOTf were used.

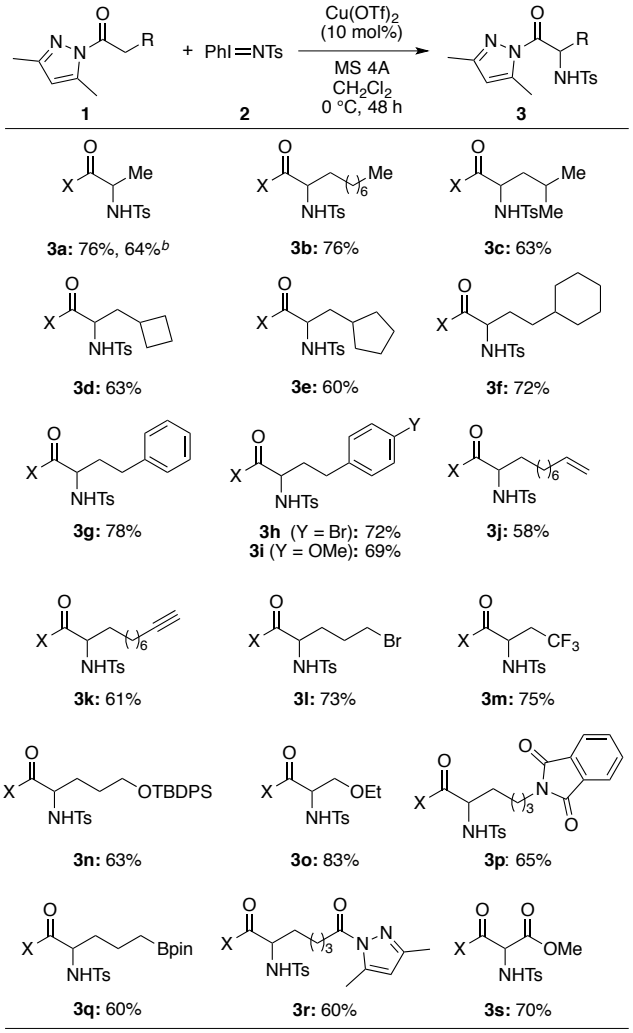
Scheme 3. Evaluation of Carboxylic Acid Oxidation State Pronucleophiles





We next investigated the substrate scope of acylpyrazoles using copper(II) triflate as an optimal catalyst (Table 2).[16] Under the optimized conditions, we observed wide functional group tolerance. The present catalysis could be run in gram scale without a significant loss of yield (**3a**). A variety of alkyl chains could be incorporated (**3b**–**3f**). Homophenylalanine derivatives were obtained in high yield with benzylic position intact (**3g**–**3i**).[15] Notably, terminal alkene, a suitable substrate for aziridination, survived the present catalysis (**3j**).[7a] Alkyl halide, ether, phthalimide, and boronate ester functionalities were incorporated without significant detrimental effects to the chemical yield (**3l**–**3q**), thus highlighting the wide functional group compatibility of the present α-amination reaction. A bis-acylpyrazole substrate selectively provided a monoaminated product (**3r**). A readily enolizable malonate derivative could be converted in high yield into **3s**, which is amenable to further differential elaboration of acylpyrazole and ester functionalities.

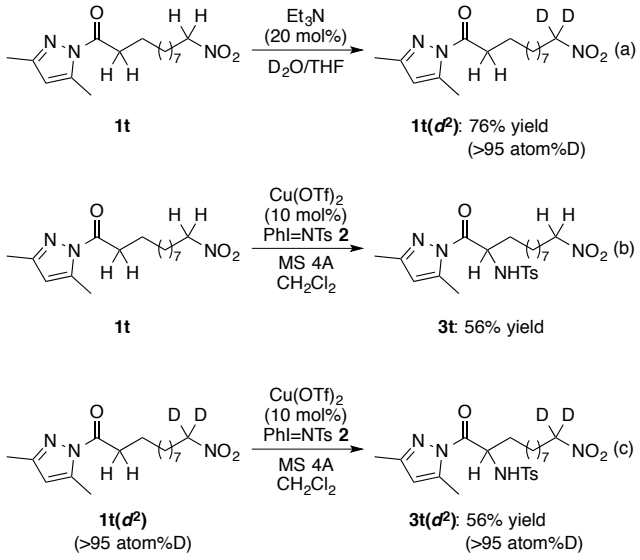
Table 2. Substrate Scope of Acylpyrazole[a]



[a]Conditions: **1** (0.4 mmol), **2** (0.2 mmol). Isolated yields are shown. [b]Gram scale synthesis (5.31 mmol scale). X stands for 3,5-dimethylpyrazolyl group.

To demonstrate the chemoselective nature of the present catalysis, deuterium exchange experiments were conducted (Scheme 4). We selected a substrate with a nitroalkyl functionality, **1t**, as a model substrate. When **1t** was treated with a catalytic amount of mildly basic triethylamine in D_2O/THF, we exclusively obtained a di-deuterated product at the α-position of nitro functionality (Scheme 4-a).[17] This result clearly indicated that the α-proton of the nitroalkyl functionality was inherently more acidic than the corresponding acylpyrazole, and nitronate was exclusively formed under even mildly basic conditions.[18] In sharp contrast, the amination proceeded chemoselectively at the α-position of acylpyrazole over the nitroalkyl functionality under our standard conditions (Scheme 4-b). Moreover, when deuterated **1t(*d*^{2})** was subjected to the standard conditions, **3t(*d*^{2})** was observed without a decrease in the deuterium ratio of the nitroalkyl functionality, suggesting that exclusive enolization of acylpyrazole was achieved under the standard conditions without the formation of a nitronate.[11] This is the first catalytic chemoselective deprotonative activation method of a carboxylic acid oxidation state pronucleophile over a highly acidic nitroalkyl functionality.

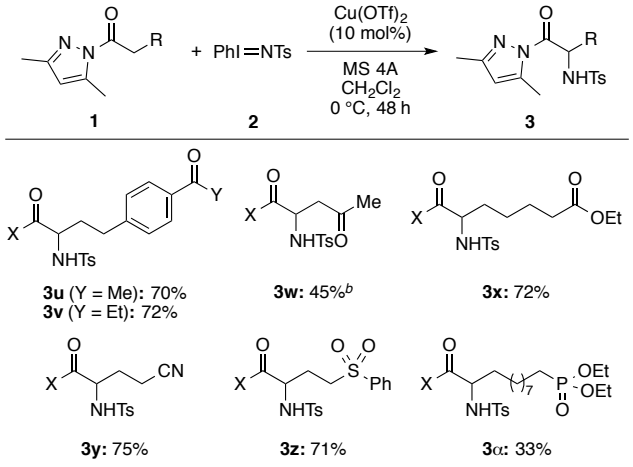
Scheme 4. Chemoselective Enolization of Acylpyrazole over Highly Reactive Nitroalkyl Functionality



Acylpyrazole, having an aryl ketone and other electron withdrawing functionalities, was then subjected to the optimized conditions to further demonstrate the chemoselective nature of the present catalysis (Table 3). When keto-acylpyrazoles **1u** and **1v** were used, the amination reaction proceeded exclusively at the α-position of acylpyrazole and the corresponding products (**3u** and **3v**) were isolated in high yield.[19] Chemoselective α-amination also proceeded with acylpyrazole **1w** derived from levulinic acid, whereas levulinic acid derivatives commonly afforded β/δ-aminated product via bromination.[20] Other electron-withdrawing groups were also applicable and the desired products were obtained chemoselectively (**3y** and **3z**). Highly coordinative phosphate substrate **1α** afforded the product **3α** in moderate yield, presumably

because the competitive coordination of phosphate functionality disturbs the efficient enolization of acylpyrazole

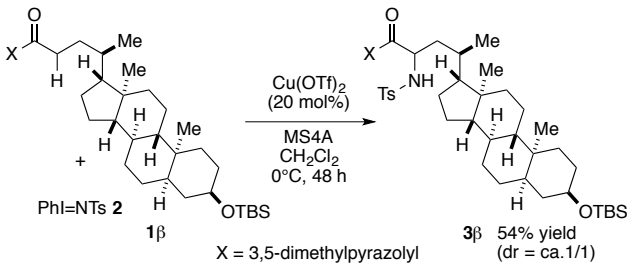
Table 3. Substrate Scope for Chemoselective α-Amination[a]



[a]Conditions: **1** (0.4 mmol), **2** (0.2 mmol). Isolated yields are shown. [b]20 mol% $Cu(OTf)_2$. X stands for 3,5-dimethylpyrazolyl group.

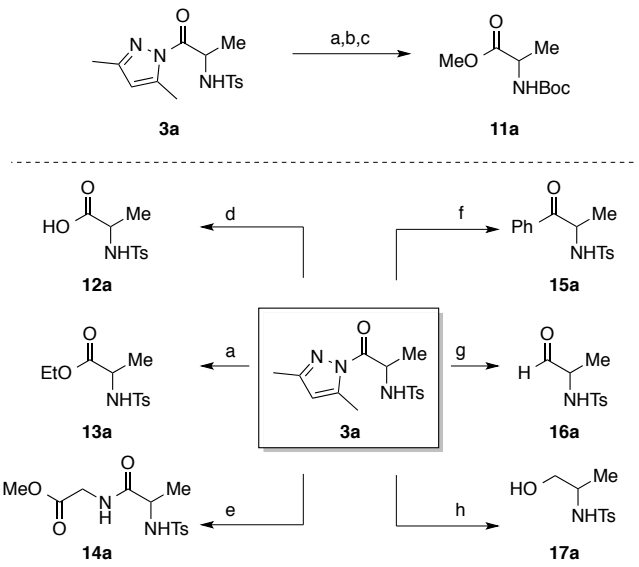
Our catalytic α-amination was applied to late-stage α-amination (Scheme 5). TBS-protected lithocholic acid derivative **1β** was converted into the corresponding α-amino acid derivative **3β** ⓘ● a synthetically useful yield in the presence of 20 mol% catalyst, indicating that the present catalysis was applicable to late-stage α-amination of complex molecules.

Scheme 5. Late-Stage α-Amination of Lithocholic Acid Derivative



Deprotection of the tosyl group of **3a** was achieved, and the corresponding *N*-Boc protected amino ester **11a** was obtained in high yield (Scheme 6), while, in previous catalytic α-amination of α-aryl pronucleophiles, further elaboration of the products into primary amines seemed to be difficult.[7f-7h] In addition, the acylpyrazole functionality was transformed into various functional groups, such as carboxylic acid, ester, ketone, aldehyde, and alcohol in high yield.[9b] It is noteworthy that direct peptide coupling was also achieved by treatment with glycine ester without any condensation reagent (**14a**).[21]

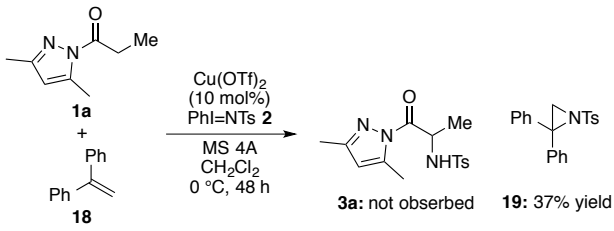
Scheme 6. Divergent Transformation of the Product



Reaction conditions: (a) NaOEt, EtOH, rt, 99% yield. (b) $(Boc)_2O$, DMAP, Et_3N, DCM, 0 °C, quant. (c) Mg, MeOH, sonication, rt, 99% yield. (d) NaOH, H_2O/MeOH, rt, 97% yield. (e) H-Gly-OMe HCl, NEt_3, toluene, 50 °C, quant. (f) PhMgBr, Et_2O, 0 °C to rt, 94% yield. (g) $LiAlH_4$, THF, –40 °C, 83% yield. (h) $NaBH_4$, H_2O/THF, rt, quant.

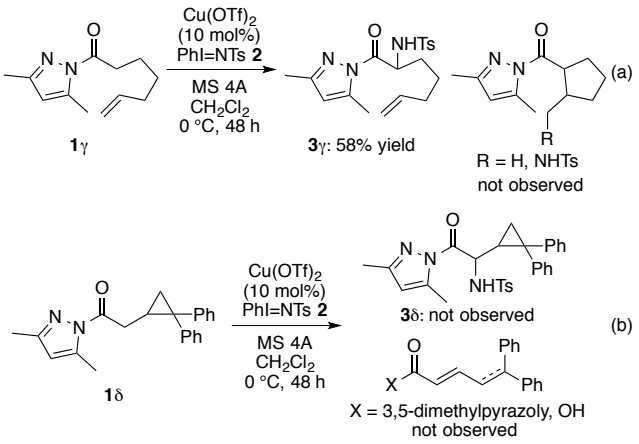
To gain preliminary mechanistic insight, we performed several control experiments. Addition of 1,1-diphenylethylene (**18**) to the standard conditions completely terminated the reaction; instead, 2,2-diphenylaziridine **19** was obtained as a by-product, suggesting the generation of highly reactive copper nitrenoid (Scheme 7).[22,23] This finding was also consistent with the poor results obtained Lewis acid (Zn, Sc: Table 1, entries 3 and 4) or Brønsted acid (Table 1, entries 5 and 6) as a catalyst.[24]

Scheme 7. Confirmation of Copper Nitrenoid Formation



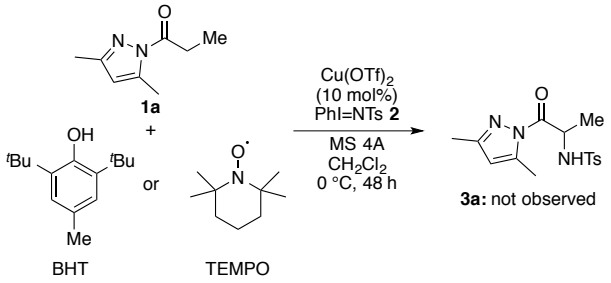
To confirm whether the reaction involved an α-carbon radical intermediate, substrate **1γ** having a terminal olefin at the 5-exo position was subjected to the standard conditions (Scheme 8-a). In this reaction, only the usual α-aminated product **3γ** was observed and no cyclized product was detected in the crude reaction mixture.[25] When α-cyclopropyl substrate **1δ** was subjected to the standard conditions, we detected no ring-opened products (Scheme 8-b).[25,26] These findings indicated that an α-radical intermediate was not involved in the present catalysis.

Scheme 8. Radical Clock Experiments with 1γ and 1δ



On the other hand, the intermediacy of the radical species was supported by radical scavenger addition experiments (Scheme 9). The desired α-aminations were completely terminated by adding a stoichiometric amount of BHT or TEMPO.[27] We speculated that copper nitrenoid species with a radical character would be generated, followed by stepwise transient aziridine formation.[28-30]

Scheme 9. Addition of Radical Scavengers



Conclusion

In conclusion, we developed a Lewis acidic copper catalyzed chemoselective α-amination by combining acylpyrazole and iminoiodinane. Noteworthy is that α-amination of acylpyrazole exclusively proceeded over much more acidic nitroalkyl functionalities, which could be easily activated even by a catalytic amount of mild base. Our method offers concise access to previously untouched unnatural α-amino acids through late-stage α-amination. Further applications of acylpyrazole as a carboxylic acid oxidation state pronucleophile for late-stage functionalization and the development of enantioselective variants are in progress.[31]

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

yazaki@phar.kyushu-u.ac.jp
ohshima@phar.kyushu-u.ac.jp

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was financially supported by Grant-in-Aid for Scientific Research (B) (#24390004), Young Scientists (B) (#26860012), Exploratory Research (#15K14930), Scientific Research on Innovative Area 2707 Middle molecular strategy and Platform for Drug Discovery, Informatics, and Structural Life Science from MEXT. R.Y thanks Ube Industries, Ltd. Award in Synthetic Organic Chemistry, Japan, Shorai Fundation for Science and Technology and The Society of Iodine Science. We are grateful to Dr. Kensuke Kiyokawa at Osaka University and Dr. Akira Yoshimura at University of Minnesota Duluth for fruitful discussion regarding iminoiodinane synthesis.

REFERENCES

(1) (a) Cornish, V. W.; Mendel, D.; Schultz, P. G. *Angew. Chem. Int. Ed.* **1995**, *34*, 621. (b) Renner, M. K.; Shen, Y.-C.; Cheng, X.-C.; Jensen, P. R.; Frankmoelle, W.; Kauffman, C. A.; Fenical, W.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1999**, *121*, 11273. (c) van Maarseveen, J. H.; Back, J. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5926. (d) Wang, L.; Schultz, P. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 34. (e) Gilmartin, A. G.; Faitg, T. H.; Richter, M.; Groy, A.; Seefeld, M. A.; Darcy, M. G.; Peng, X.; Federowicz, K.; Yang, J.; Zhang, S.-Y.; Minthorn, E.; Jaworski, J.-P.; Schaber, M.; Martens, S.; McNulty, D. E.; Sinnamon, R. H.; Zhang, H.; Kirkpatrick, R. B.; Nevins, N.; Cui, G.; Pietrak, B.; Diaz, E.; Jones, A.; Brandt, M.; Schwartz, B.; Heerding, D. A.; Kumar, R. *Nat. Chem. Biol.* **2014**, *10*, 181.

(2) (a) Rutjes, F. P. J. T.; Wolf L. B.; Schoemaker, H. E. *J. Chem. Soc., Perkin Trans*. **2000**, *1*, 4197. (b) Kaiser, J.; Kinderman, S. S.; van Esseveldt, B. C. J.; van Delft, F. L.; Schoemaker, H. E.; Blaauw, R. H.; Rutjes, F. P. J. T. *Org, Biomol. Chem*. **2005**, *3*, 3435. (c) Perdih, A.; Dolenc, M. S. *Curr. Org. Chem*. **2007**, *11*, 801. (d) Perdih, A.; Dolenc, M. S. *Curr. Org. Chem*. **2011**, *15*, 3750.

(3) (a) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795. (b) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117. (b) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968. (d) Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* **2011**, *111*, 6947.

(4) (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (d) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656. (e) Jew, S.-S.; Park, H.-G. *Chem. Commun.* **2009**, 7090.

(5) (a) Erdik, E. *Tetrahedron*, **2004**, *60*, 8747. (b) Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org Chem*. **2004**, 1377. (c) Janey, J. M. *Angew. Chem. Int. Ed*. **2005**, *44*, 4292. (d) Marigo, M.; Jørgensen, K. A. *Chem. Commun*. **2006**, 2001. (e) Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, *111*, 1637. (d) Zhou, F.; Liao, F.-M.; Yu, J.-S.; Zhou, J. *Synthesis* **2014**, *46*, 2983.

(6) (a) Shenvi, R. A.; O'Malley, D. P.; Baran, P. S. *Acc. Chem. Res.* **2009**, *42*, 530. (b) Ishihara, Y.; Baran, P. *Synlett* **2010**, *12*, 1733.

(7) Recent examples of catalytic α-amination of carboxylic acid oxidation state substrates. ketene silyl acetals: (a) Evans, D. A.; M.; Bilodeau, M. T.; Faul M. M. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (b)

Tanaka, M.; Kurosaki, Y.; Washio, T.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2007**, *48*, 8799. (c) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 11827. (d) Miura, T.; Morimoto, M.; Murakami, M. *Org. Lett.* **2012**, *14*, 5214. (e) Sandoval, D.; Samoshin, A. V; Read de Alaniz, J. *Org. Lett.* **2015**, *17*, 4514. α-Aryl esters: (f) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452. (g) Zhao, B.; Du, H.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 7220. (h) Evans, R. W.; Zbieg, J. R.; Zhu, S.; Li, W.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 16074. α-bromo esters: (i) Fisher, D. J.; Burnett, G. L.; Velasco, R.; Read de Alaniz, J. *J. Am. Chem. Soc.* **2015**, *137*, 11614.

(8) Late-stage catalytic nucleophilic addition of carboxylic acid to imine: Morita, Y.; Yamamoto, T.; Nagai, H.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2015**, *137*, 7075.

(9) (a) Kashima, C.; Fukuchi, I.; Hosomi, A. *J. Org. Chem.* **1999**, *59*, 7821. (b) Kashima, C. *Heterocycles.* **2003**, *60*, 437. α-Aryl acylpyrazoles in organocatalysis, see: (c) Tan, B.; Hernández-Torres, G.; Barbas III, C. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 5381. (d) Li, T.-Z.; Wang, X.-B.; Sha, F.; Wu, X.-Y. *J. Org. Chem* **2014**, *79*, 4332.

(10) See Supporting Information.

(11) Driessen, W. L.; Everstijn, P. L. A. *Inorg. Chim. Acta*. **1980**, *41*, 179.

(12) In reference 7a, the authors concluded that α-amination of ketene silyl acetals using iminoiodinane was not practical for α-amino ester synthesis. For the preparation of iminoiodinane, see; Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361.

(13) Other aminating agents, such as hydroxylamine derivatives and nitroso compounds proved to be insufficient. We also evaluated other iminoiodinane derivatives (PhI=NR; R = Ns, Ses). However the inferior results were obtained.

(14) Catalytic α-amination of pre-activated ketones or active methylene compounds using iminoiodinanes, see: (a) Adam, W.; Roschmann, K. J.; Saha-Möller, C. R. *Eur. J. Org. Chem.* **2000**, 557. (b) Liang, J.-L.; Yu, X.-Q.; Che, C.-M. *Chem. Commun.* **2002**, 124. (c) Anada, M.; Tanaka, M.; Washio, T.; Yamawaki, M.; Abe, T.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 4559. (d) Tanaka, M.; Nakamura, S.; Anada, M.; Hashimoto, S. *Heterocycles.* **2008**, *76*, 1633. (e) Nakanishi, M.; Salit, A.-F.; Bolm, C. *Adv. Synth. Catal.* **2008**, *350*, 1835. (f) Chang, J. W. W.; Ton, T. M. U.; Chan, P. W. H. *Chem. Rec.* **2011**, *11*, 331. (g) Yu, J.; Liu, S.-S.; Cui, J.; Hou, X.-S.; Zhang, C. *Org. Lett.* **2011**, *14*, 832. (h) Ton, T. M. U.; Himawan, F.; Chang, J. W. W.; Chan, P. W. H. *Chem. Eur. J.* **2012**, *18*, 12020. (i) Tejo, C.; Yeo, H. Q.; Chan, P. W. H. *Synlett.* **2014**, *25*, 201.

(15) Recent reviews on copper-catalyzed aminations, see; (a) Gephart, R. T.; Warren, T. H. *Organometallics* **2012**, *31*, 7728. (b) Yan, X.; Yang, X.; Xi, C. *Catal. Sci. Technol*. **2014**, *4*, 4169.

(16) A certain amount of acylpyrazole was decomposed during the course of reaction. When 1.5 equivalent of **1a** was used, amination product **3a** was observed in 59% yield.

(17) Smirnov, V. O.; Khomutova, Y. A.; Tartakovsky, V. A.; Ioffe, S. L. *Eur. J. Org. Chem.* **2012**, 3377.

(18) Nitroalkane is known to be much more acidic than ketone and preferential nitronate formation was observed over ketone even under mildy basic conditions, see: (a) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975***, 97*, 7006. (b) Do, H.-Q.; Tran-vu, H.; Daugulis, O. *Organometallics* **2012**, 31, 7816.

(19) Chemoselective deprotonative activation of thioamides over ketones: Iwata, M.; Yazaki, R.; Chen, I.-H.; Sureshkumar, D.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5554. Also see Ref. 8

(20) Treatment of levurinic acid derivatives with bromine afforded mixture of β/δ-brominated products and no α-brominated product was obtained. (a) MacDonald, S. F. *Can. J. Chem*. **1974**, *52*, 3257. (b) Sorg, A.; Siegel, K.; Brückner, R. *Chem. Eur. J* **2005**, *11*, 1610. (c) Zavozin, A. G.; Ignat'ev, N. V.; Schulte, M.; Zlotin, S. G. *Tetrahedron* **2013**, *69*, 6975.

(21) Kashima, C.; Tsuruoka, S.; Mizuhara, S. *Heterocycles.* **2000** *52*, 413.

(22) (a) Badiei, Y. M.; Krishnaswamy, A.; Melzer, M. M.; Warren, T. H. *J. Am. Chem. Soc.* **2006**, 128, 15056. (b) Badiei, Y. M.; Dinescu, A.; Dai, X.; Palomino, R. M.; Heinemann, F. W.; Cundari, T. R.; Warren, T. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 9961. (c) Wiese, S.; Badiei, Y. M.; Gephart, R. T.; Mossin, S.; Varonka, M. S.; Melzer, M. M.; Meyer, K.; Cundari, T. R.; Warren, T. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 8850.

(23) We also observed α-aminated product of THF when reaction was performed in THF. Copper-nitrenoid species were proposed in α-amination of cyclic ether, see: He, L.; Yu, J.; Zhang, J.; Yu, X.-Q. *Org. Lett.* **2007**, *9*, 2277.

(24) Without molecular sieves, low chemical yield was observed with significant amount of generation of $TsNH_2$ by hydrolysis of the copper nitrenoid.

(25) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc*. **2008**, *130*, 11546

(26) Amaya, T.; Maegawa, Y.; Masuda, T.; Osafune, Y.; Hirao, T. *J. Am. Chem. Soc.* **2015**, *137*, 10072.

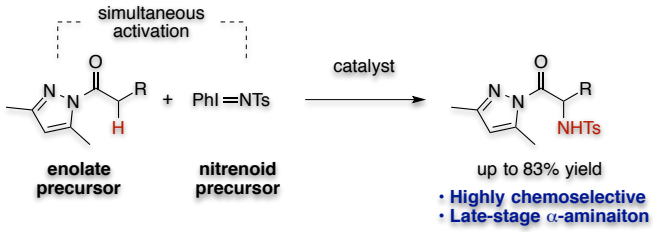
(27) When TEMPO was added to reaction mixture, α-oxyaminated product was observed by LC-MS analysis in the crude reaction mixture. We speculated that α-oxyamination proceeded through enolate addition to 2e electrophilic Cu-TEMPO complex, see: (a) Michel, C.; Belanzoni, P.; Gamez, P.; Reedjik, J.; Baerends, E. J. *Inorg. Chem*. **2009**, *48*, 11909. (b) van Humbeck, J. F.; Simonovich, S. P.; Knowles, R. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10012.

(28) (a) Díaz-Requejo, M. M.; Pérez, P. J.; Brookhart, M.; Templeton, J. L. *Organometallics* **1997**, *16*, 4399. (b) Brandt, P.; Södergren, M. J.; Andersson, P. G.; Norrby, P.-O. *J. Am. Chem. Soc.* **2000**, *122*, 8013. (c) Gómez-Emeterio, B. P.; Urbano, J.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics* **2008**, *27*, 4126. (d) Maestre, L.; Sameera, W. M. C.; Díaz-Requejo, M. M.; Maseras, F.; Pérez, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 1338. (e) Bagchi, V.; Paraskevopoulou, P.; Das, P.; Chi, L.; Wang, Q.; Choudhury, A.; Mathieson, J. S.; Cronin, L.; Pardue, D. B.; Cundari, T. R.; Mitrikas, G.; Sanakis, Y.; Stavropoulos, P. *J. Am. Chem. Soc.* **2014**, *136*, 11362. Also see the possible involvement of radical species in amination reaction; (f) Ton, T. M. U.; Tejo, C.; Tiong, D. L. Y.; Chan, P. W. H. *J. Am. Chem. Soc.* **2012**, *134*, 7344. and Ref 14h

(29) The possibility of inhibition of enolization by radical scavengers and concerted mechanism cannot be ruled out.

(30) A reviewer suggested directed C-H amination serving acylpyrazole as directing group as a possible alternative mechanism.

(31) When chiral substrate **3a** was subjected to the reaction conditions, no racemization was observed.


simultaneous activation
catalyst
PhI=NTs
NHTs
enolate precursor
nitrenoid precursor
up to 83% yield
• Highly chemoselective
• Late-stage α-aminaiton