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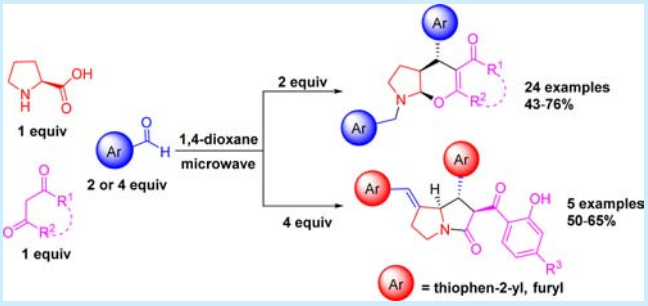
Microwave-Promoted, Metal- and Catalyst-Free Decarboxylative α,β-Difunctionlization of Secondary α-Amino Acids via Pseudo-Four-Component Reactions

Kiran B. Manjappa, Wei-Fang Jhang, Shin-Yi Huang, and Ding-Yah Yang*

Department of Chemistry, Tunghai University, No. 1727, Sec. 4, Taiwan Boulevard, Xitun District, Taichung City 40704, Taiwan, Republic of China

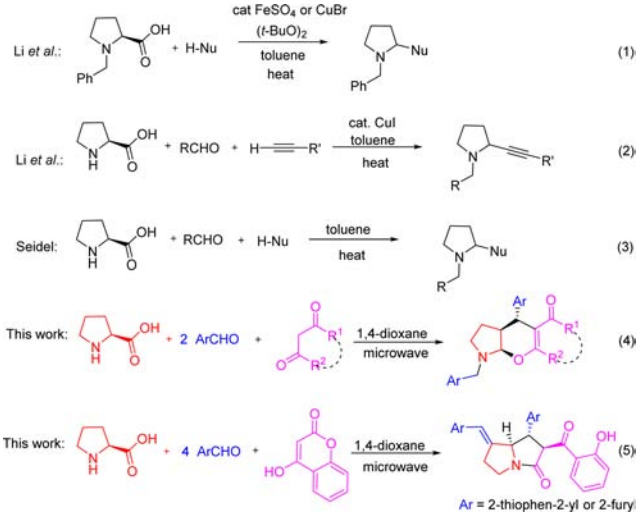
Supporting Information

ABSTRACT: A microwave-promoted, metal- and catalyst-free decarboxylative α,β-difunctionlization of secondary α-amino acids via a pseudo-four-component coupling of proline, aldehyde, and 1,3-diketone to generate multifunctionalized pyrano[2,3-*b*]pyrrole and pyrrolizinone derivatives is reported.



Decarboxylative α-functionalizations of α-amino acids with carbonyl compounds (also known as the Strecker degradation[1]) are of interest to chemists in the field of derivatization of α-amino acids since the reaction leads to the facile preparation of amine derivatives by replacing the carboxyl group of α-amino acids with various functionalities.[2] The key intermediates of this reaction have been identified as azomethine ylides,[3] which can readily undergo either inter- or intramolecular [3 + 2] cycloadditions with alkynes, alkenes, or ketones to give diverse nitrogen-containing 5-membered ring heterocycles.[4] Recently, several new strategies employing nonpericyclic reaction of azomethine ylides for the preparation of decarboxylative α-functionalized amino acids have emerged. For instance, Li et al.[5] have reported a C−C bond-forming reaction based on a CuBr- or $FeSO_4$-catalyzed oxidative decarboxylative coupling of sp- or sp^2-hybridized carbons with *N*-benzylproline using *tert*-butyl peroxide as the oxidant (eq 1, Scheme 1). The same group[6] has also described a CuI-catalyzed aldehyde- or ketone-induced tandem decarboxylation−coupling of natural α-amino acids and terminal alkynes (eq 2, also termed as the decarboxylative A^3 reaction[7]). Very recently, Seidel and Zhang[8] have reported a catalyst-free, three-component coupling reaction among proline, aldehyde, and nucleophiles such as β-naphthols, indoles, or nitroalkanes (eq 3). These tandem decarboxylation−nucleophilic addition reactions represent useful strategies for efficient conversion of α-amino acids to the corresponding α-functionalized amine derivatives. Nevertheless, methods for the preparation of α,β-difunctionlized amines via decarboxylation of secondary α-amino acids utilizing tandem decarboxylation−electrophilic addition reactions are much less explored. As part of our continuing efforts[9] toward the preparation of molecules with novel molecular skeletons via multicomponent reactions (MCRs), we report a metal- and catalyst-free decarboxylative α,β-difunctionlization of secondary α-amino acids via pseudo-four-component coupling of proline, aldehyde, and 1,3-diketone under microwave irradiation to generate multifunctionalized pyrano[2,3-*b*]pyrroles (eq 4) and pyrrolizinones (eq 5). The scope and limitation of this synthetic methodology are investigated, and the possible mechanisms for the product formation are proposed.

Scheme 1



We initiated our studies by investigating the reaction among proline, benzaldehyde, and 4-hydroxycoumarin. Simple heating

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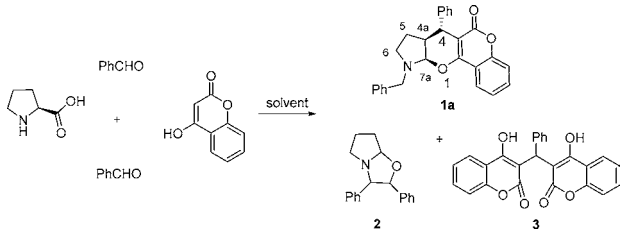
Table 1. Optimization of Reaction Parameters for 1a



entry	solvent	temp (°C)	time (h)	yield[a] (%) 1a	2	3
1	toluene	130	1	35	15	28
2	toluene	130	2	28	23	30
3	CH3CN	130	5	≥5	trace	trace
4	THF	130	5	≥5	trace	trace
5	1,4-dioxane	130	1	47	≥5	none
6	1,4-dioxane	130	5	49	≥5	none
7	DCE	130	5	20	trace	trace
8	EtOH	130	5	trace	none	none
9	H2O	130	30 min	none	none	none
10	xylene	130	1	10	35	20
11	toluene	150/150 W	10 min	45	trace	trace
12	toluene	150/200 W	15 min	48	trace	trace
13	toluene	200/200 W	10 min	50	trace	trace
14	1,4-dioxane	200/200 W	15 min	53	trace	trace
15	xylene	150/200 W	15 min	35	≥10	≥30
16	xylene	200/200 W	10 min	≥30	≥15	≥30
17	nitrobenzene	200/200 W	10 min	trace	≥25	≥20

[a]Isolated yield with 70−85% proline conversions. All reactions were conducted in 35 mM proline concentration.

of a mixture of the three components in toluene under refluxing conditions for 1 h led to the formation of the pyrano[2,3-*b*]pyrrole **1a**, pyrrolo[2,1-*b*]oxazole **2**, and 3,3′-(phenylmethylene)bis(4-hydroxycoumarin) (**3**) in 35, 15, and 28% yield, respectively. The reaction was further carried out in various solvents and temperatures in search of the conditions that can minimize the formation of the undesired products **2** and **3**. Table 1 summarizes the optimization results for the synthesis of **1a** via a multicomponent reaction (MCR). Among the solvents examined, xylene was found to be the most effective one for reactions performed under thermal conditions. Solvents such as THF and CH_3CN with boiling points lower than 100 °C generally gave much lower yields (entries 3 and 4). More polar solvents such as EtOH and H_2O gave no desired product formation at all (entries 8 and 9). Furthermore, prolonged reaction time did not increase the yields accordingly (entries 6−8). As for reactions carried out under microwave irradiation (200 W, 200 °C, 15 min), 1,4-dioxane was found to be the best solvent. Compared to thermal reactions, microwave irradiation gave better yields and higher proline conversions. Thus, the microwave conditions (entry 14) were employed subsequently for all further reactions.

Figure 1 lists the structures and yields of the pyrano[2,3-*b*]pyrroles **1a−m**, **s−x** and pyrano[2,3-*b*]pyridines **1n−r** prepared by MCR. A total of 24 examples are given with 43−76% isolated yields and 80−85% proline conversions. According to Figure 1, pipecolic acid can also be served as an alternative substrate for proline in these pseudo-four-component reactions (**1n−r**). While aromatic aldehydes with either an electron-donating (OMe) or -withdrawing (NO_2) group at the *para* position of the benzene ring proved to be viable substrates, *ortho*-substituted aromatic aldehydes and aliphatic aldehydes generally gave complicated mixtures with much lower yields. For the third substrate 1,3-diketone, 7-(*N*,*N*-dimethylamino)-4-hydroxycoumarin generally gave better yields than those of 4-hydroxycoumarin and dimedone. The molecular structures of those prepared compounds were fully elucidated by spectroscopic data. In the ^1H NMR spectra, a characteristic small doublet (J = 3.3−3.9 Hz) absorption peak at the chemical shift between 5.03 and 5.33 ppm, which was assigned to the 7a-H in the pyrano[2,3-*b*]pyrrole ring, was observed for all prepared compounds (see **1a** in Table 1 for atom numbering). Some of the heterocyclic structures (**1a** and **1p**) were further characterized by the X-ray crystal analysis as shown in Figure 2. In addition to the formation of two C−C bonds, one C−N bond, and one C−O bond in the final product, this pseudo-four-component reaction was found to be stereoselective, creating a bicyclic system that contains three chiral centers with 7a-H and 4a-H *cis* to each other, while 4a-H and 4-H are *trans*. Furthermore, the bond formation during the construction of the pyrano[2,3-*b*]pyrrole and pyrano[2,3-*b*]pyridine skeleton is atom-economical, with a total mass loss of only 80 g/mol, which is attributed to the release of one molecule of carbon dioxide and two molecules of water as the byproducts.

In an effort to drive the proline conversions to completion, an excess of thiophene or furan carbaldehyde (4 equiv) was added to the reaction with 4-hydroxycoumarin. Surprisingly, a new major product **4** was obtained along with the expected minor product **1**. This unexpected product **4** was isolated and found to be a pyrrolizinone derivative (eq 5 in Scheme 1). Figure 3 lists the structures and yields of the pyrrolizinones **4a−e** prepared by the MCR. The molecular structure of **4a** was characterized by the X-ray crystal analysis as shown in Figure 4.

Interestingly, formation of the pyrrolizinone products could only be observed when thiophene or furan carbaldehyde was used

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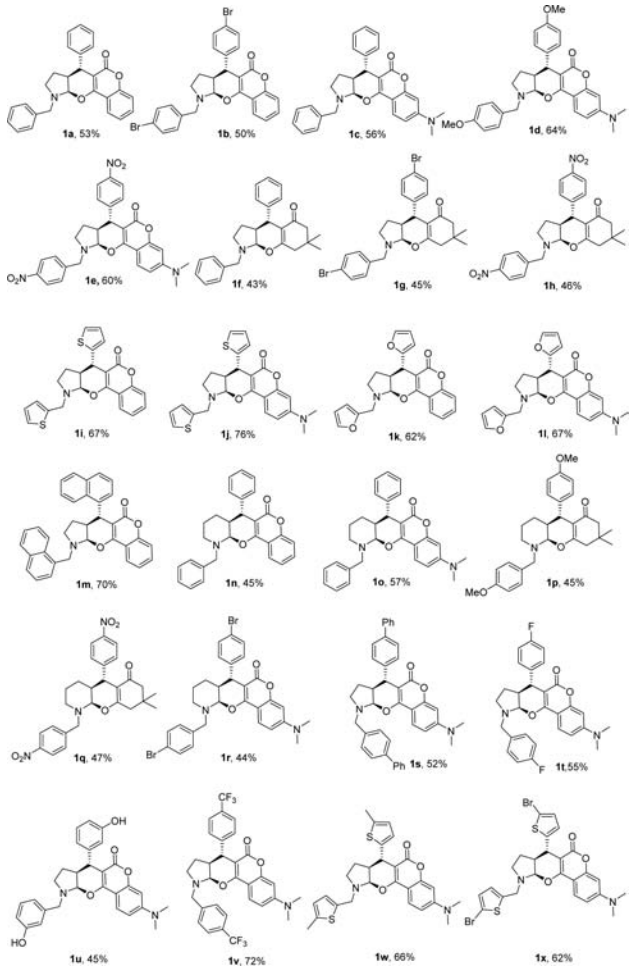


Figure 1. Structures of the prepared compounds **1a**−**x**.

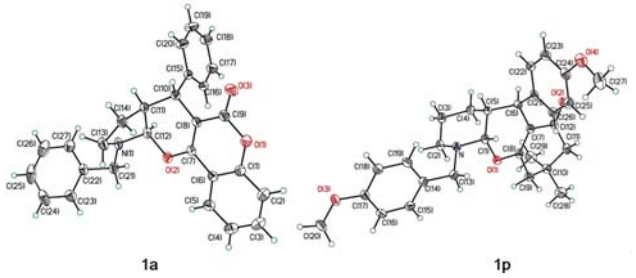


Figure 2. ORTEP crystal structures of **1a** and **1p**.

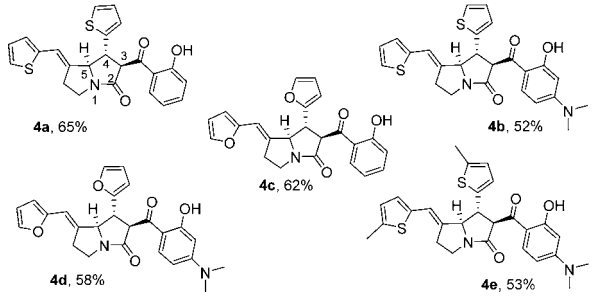


Figure 3. Structures of the prepared compounds **4a**−**e**.

as the substrate. Other aromatic aldehydes such as substituted benzaldehydes all failed to give any corresponding compounds **4**. The formation of **4** was also found to be stereoselective, creating a

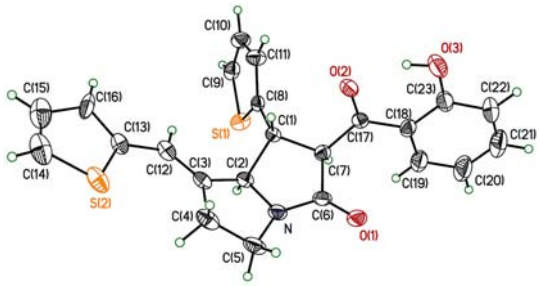
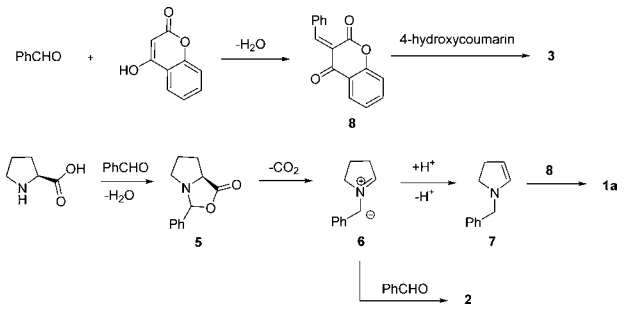


Figure 4. ORTEP crystal structure of **4a**.

bicyclic system that contains three chiral centers with 3-H, 4-H, and 5-H *trans* to each other (see **4a** in Figure 3 for atom numbering). Similar to **1**, the bond formation during the construction of the pyrrolizinone scaffold is highly atom-economical, generating one C═C bond, two C−C bonds, and one C−N bond in the final product. The fact that both pyrano[2,3-*b*]pyrrole **1** and pyrrolizinone **4** contain a bicyclic skeleton and share the same molecular formula/weight indicates that they are the more stable thermodynamic products than any other possible intermediates in this multistep reaction.

Scheme 2 depicts a plausible mechanism for the formation of **1a**, **2**, and **3** from the pseudo-four-component coupling reaction.

Scheme 2



It begins with the condensation of proline with benzaldehyde to yield the oxazolidin-5-one **5**,[10] a known intermediate in the subsequent decarboxylative formation of the azomethine ylide **6**. The resulting ylide **6** can either react with benzaldehyde via the [3 + 2] cycloaddition to give the undesired product **2**[11] or undergo proton-mediated isomerization to afford the enamine **7**. The proton source for this isomerization presumably may come from either *α*-amino acid or 1,3-diketone. Final conjugate addition of the enamine **7** to *α*,*β*-unsaturated ketone **8** (generated in situ by condensation of 4-hydroxycoumarin and benzaldehyde) and subsequent intramolecular cyclization yield the desired product **1a**. As for compound **3**, it is likely formed by conjugate addition of 4-hydroxycoumarin to *α*,*β*-unsaturated ketone **8**.[12] This proposed mechanism can also explain the fact that complex product mixtures were observed when aliphatic aldehydes were used as the substrate in this reaction since more than one possible enamine isomers could be formed from the azomethine ylide intermediates.

Scheme 3 depicts the proposed mechanism for the formation of **4a**. First, the microwave-promoted generated enamine **9** attacks thiophene carbaldehyde to give the alcohol **10** and follows by dehydration to yield the condensed *α*,*β*-unsaturated iminium **11**. The second step involves H_2O-mediated Michael addition of **11** to **12** (generated in situ by condensation of 4-hydroxycou-

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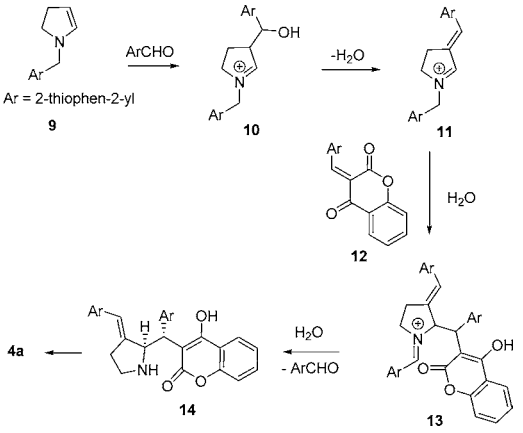
Scheme 3



marin and thiophenecarbaldehyde) to afford the intermediate **13**. The subsequent hydrolysis of the iminium **13** gives the free amine **14**. Final intramolecular nucleophilic acyl substitution to open the lactone ring on the coumarin moiety by the amine nearby furnishes the product lactam **4a**. Since at least 3 equiv of thiophenecarbaldehyde are needed for the formation of the iminium **13**, this mechanism supports the observation that the formation of **4a** is favored when a higher concentration of aldehyde is present in the reaction. It is worth mentioning that this readily available pyrrolizinone **4** can presumably serves as a precursor for efficient synthesis of some naturally occurring and biologically important pyrrolizidine alkaloids (necine bases).[13]

Our studies demonstrate that the azomethine ylide intermediates, generated via microwave-promoted decarboxylative coupling of proline and aromatic aldehyde, can undergo proton-mediated isomerization to the enamine **7** or **9**. The enamine can then proceed to two different products via two different pathways, depending upon the concentration and size of the aldehyde present in the reaction. First, the enamine **7** can undergo conjugate addition to **8** and subsequent cyclization to yield pyrano[2,3-*b*]pyrrole **1**. Second, the enamine **9** can condense with aldehyde and then followed by conjugate addition to **12** to afford pyrrolizinone **4**. Pyrano[2,3-*b*]pyrrole **1** is formed exclusively when 2 equiv of aldehyde is present in the reaction, whereas pyrrolizinone **4** is favored predominantly when 4 equiv of thiophene or furan carbaldehyde is present. Thus, we have discovered a new mode of reactivity for azomethine ylides other than the well-documented [3 + 2] cycloaddition and protonation/nucleophilic addition. This MCR synthetic strategy represents one of the few methods of the preparation of α,β-difunctionlized amines via decarboxylation of secondary α-amino acids.[14]

In summary, we have reported a metal- and catalyst-free synthesis of multifunctionalized pyrano[2,3-*b*]pyrrole, pyrano-[2,3-*b*]pyridine, and pyrrolizinone derivatives via a pseudo-four-component coupling of proline/pipecolic acid, 2 or 4 equiv of aldehyde, and 1,3-diketone in 1,4-dioxane under microwave irradiation. We also found that the product distributions of **1** and **4** can be controlled by varying the concentration and size of the aromatic aldehyde added into the reaction. Further applications of this MCR to the synthesis of some biologically active natural products as well as potential functional materials are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Synthesis of compounds **1a−x**, **2**, **3**, **4a−e**, experimental details, additional spectra, and X-ray crystal structure details for **1a**, **1p**, and **4a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: 886-4-2359-7613. Fax: 886-4-2359-0426. E-mail: yang@thu.edu.tw.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Strecker, A. *Liebigs Ann. Chem.* **1862**, *123*, 363. (b) Schonberg, A.; Moubasher, R. *Chem. Rev.* **1952**, *50*, 261.

(2) For example, see: (a) Yan, Y.; Wang, Z. *Chem. Commun.* **2011**, 9513. (b) Mao, H.; Wang, S.; Yu, P.; Lv, H.; Xu, R.; Pan, Y. *J. Org. Chem.* **2011**, *76*, 1167.

(3) Rizzi, G. P. *J. Org. Chem.* **1970**, *35*, 2069.

(4) For selected reviews, see: (a) Padwa, A., Ed. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, 1984; Vol. *1*, p 817. (b) Padwa, A., Ed. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, 1984; Vol. 2, p 704. (c) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley: Chichester, U.K., 2002; Vol. *59*, p 940. (d) Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105. (e) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (f) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484.

(5) (a) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 792. (b) Bi, H.-P.; Chen, W.-W.; Liang, Y.-M.; Li, C.-J. *Org. Lett.* **2009**, *11*, 3246.

(6) Bi, H.-P.; Teng, Q.; Guan, M.; Chen, W.-W.; Liang, Y.-M.; Yao, X.; Li, C.-J. *J. Org. Chem.* **2010**, *75*, 783.

(7) For a recent review, see: Seidel, D. *Org. Chem. Front.* **2014**, *1*, 426.

(8) Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 1798.

(9) (a) Lin, C. H.; Jhang, J. F.; Yang, D. Y. *Org. Lett.* **2009**, *11*, 4064. (b) Lin, C. H.; Chen, J. R.; Yang, D. Y. *J. Comb. Chem.* **2010**, *12*, 119. (c) Li, K. T.; Lin, Y. B.; Yang, D. Y. *Org. Lett.* **2012**, *14*, 1190.

(10) (a) Grigg, R.; Idle, J.; McMeekin, P.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 49. (b) Zotova, N.; Franzke, A.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 15100.

(11) (a) Orsini, F.; Pelizzoni, F.; Forte, M.; Destro, R.; Gariboldi, P. *Tetrahedron* **1988**, *44*, 519. (b) Zotova, N.; Franzke, A.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 15100.

(12) (a) Shi, D. Q.; Wang, Y. H.; Lu, Z. S.; Dai, G. Y. *Synth. Commun.* **2000**, *30*, 713. (b) Jin, T. S.; Zang, J. S.; Wang, A. Q.; Li, T. S. *Synth. Commun.* **2005**, *35*, 2339. (c) Das, B.; Thirupathi, P.; Reddy, K. R.; Ravikanyh, B.; Nagarapu, L. *Catal. Commun.* **2007**, *8*, 535. (d) Ilangovan, A.; Muralidharan, S.; Sakthivel, P.; Malayappasamy, S.; Karuppusamy, S.; Kaushik, M. P. *Tetrahedron Lett.* **2013**, *54*, 491.

(13) (a) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773. (b) Dreger, M.; Stanisławska, M.; Krajewska-Patan, A.; Mielcarek, S.; Mikołajczak, P. L.; Buchwald, W. *Herba Polym.* **2009**, *55*, 127.

(14) During the preparation of this manuscript, a "redox-neutral α,β-difunctionalization of cyclic amines" was reported; see: Chen, W.; Kang, Y. K.; Wilde, R. G.; Seidel, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 5179.