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Dirhodium(II)-Catalyzed Synthesis of *N*-(Arylsulfonyl)hydrazines by N–H Amination of Aliphatic Amines

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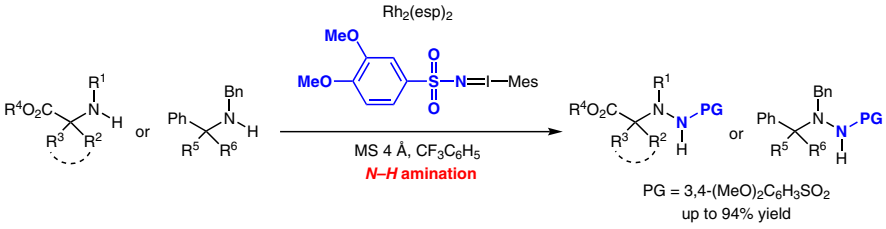

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Abstract This study reports the development of Rh(II)-catalyzed N–N bond-forming reaction of amino acid derivatives or aliphatic amines to provide hydrazine derivatives through the combined use of $Rh_2(esp)_2$ and [(3,4-dimethoxyphenyl)sulfonylimino]-2,4,6-trimethylphenyliodinane (3,4-$(MeO)_2C_6H_3SO_2N$=IMes). This is the first report of N–H amination of aliphatic amines with metal–nitrene species.

Key words amine, hydrazine, N–N bond, Rh(II) catalyst, nitrene

The nitrogen–nitrogen (N–N) bond is a privileged structural motif in natural products.[1] Among over 200 natural products containing the motif, α-hydrazino acid derivatives are of particular interest because they exhibit a diverse array of biological activities including antibacterial, anti-HCV, and immunosuppressant properties (Figure 1). α-Hydrazino acids are also prevalent in pharmaceuticals, for example, as core structures of carbidopa and cilazapril. Furthermore, their incorporation into peptides has been investigated to enhance the proteolytic stability or to control conformation.[2]

Despite their importance, the number of methods for intermolecular N–N bond formation are still limited.[3–5] In addition to classical methods including *N*-nitrosation, diazotization, and azo coupling of amines followed by reduction, electrophilic *N*-amination of amines with oxaziridine reagents is widely adopted for the synthesis of hydrazine derivatives.[2,4] Recently, some research groups have developed oxidative N–N bond formation between two distinct amines or azoles using a Cu catalyst or iodine-based oxidant as well as electrochemical oxidation.[5] However, nucleophilic and oxidation-sensitive amines are likely to cause various side reactions including dimerization via N–N, C–C, and C–N bond formation, and therefore, the combination of substrates is rather limited.

Nevertheless, electrophilic metal–nitrene species generated from metal catalysts and various nitrene precursors are capable of catalytic N–N bond formation with nitrogen-containing heteroaromatics, tertiary amines, or (sulfon)amides to form zwitterionic aminimides (N^+–N^-).[6–9] However, reactions with primary or secondary amines are underexplored due to the propensity of the highly nucleophilic substrates to poison the catalysts by strong coordination to the metal center.[10,11] Recently, we reported the synthesis of *N*-aryl-*N′*-tosyldiazenes from primary aromatic amines via N–H amination with Rh(II)–nitrene followed by oxidation (Scheme 1a).[12] To the best of our knowledge, this is the first example of N–H amination using metal–nitrene species. However, the N–H amination of more nucleophilic aliphatic amines remains a major challenge. Herein, we report the N–H amination of α-amino acid derivatives **1** or other aliphatic amines **2** using Rh(II)–nitrene to provide *N*-(arylsulfonyl)hydrazines **3** or **4** (Scheme 1b).

Initially, we performed the reactions of various *N*-alkyl-α-amino acid esters under previously reported conditions using $Rh_2(HNCOCF_3)_4$ (4 mol%) and (tosylimino)-2,4,6-

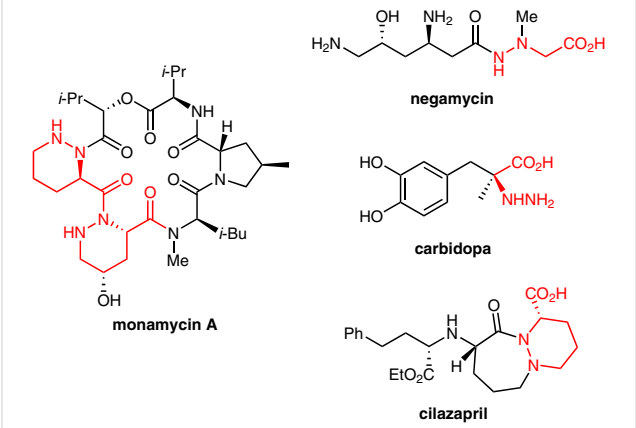

Figure 1 Natural products and pharmaceuticals containing N–N bond

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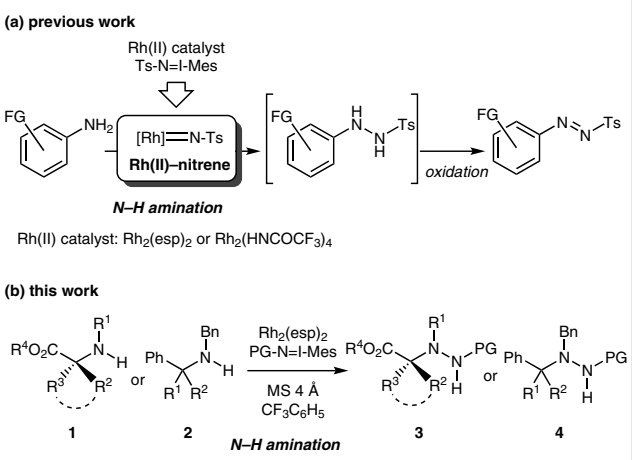
trimethylphenyliodinane (TsN=IMes, **5a**) in CH_2Cl_2 (0.025 M),[12] and found that 1-aminocyclopropanecarboxylate **1a** provided the desired α-hydrazino acid **3aa** in 51% yield (Table 1, entry 1).[13] The performance of iminoiodinanes **5b–d** bearing various arylsulfonyl groups on the nitrogen atom was also investigated (entries 2–4). Compared with TsN=IMes **5a** (entry 1), the use of *p*NsN=IMes **5b** diminished the product yield (entry 2). In contrast, introduction of the electron-donating methoxy group into the arylsulfonyl moiety significantly improved the product yield (entry 3), and product **3ad** was obtained in 88% yield by exploiting 3,4-$(MeO)_2C_6H_3SO_2N$=IMes **5d** (entry 4). With the use of **5d**, high product yields were maintained with 2 mol% loading of the catalyst (entry 5), and commercially available $Rh_2(esp)_2$ provided virtually the same result as $Rh_2(HNCOCF_3)_4$ (entry 6). Similar to our previous work, increasing the concentration of **1a** to 0.1 M led to a noticeable drop in the product yields (entry 7).[14] The solvent survey revealed that the use of $CF_3C_6H_5$ instead of CH_2Cl_2 further improved the yield of **3ad** to 94% (entries 8–11). The reaction performed on 1 mmol scale led to only a slight decrease in the product yield.[15]

With the optimized conditions at hand, we then investigated the influence of the substituent on the amino group (Table 2). The introduction of either the electron-donating or electron-withdrawing groups into the 2- or 4-position of the benzyl group had little impact on the product yield (entries 1–4). In addition to the *N*-benzyl substrates, *N*-allyl substrate **1f** uneventfully furnished product **3f** (entry 5). The bulky *N*-isopropyl group led to a significant decrease in the product yield (entry 6). Primary amine **1h** also resulted in hydrazine **3h** as the sole product in 47% yield (entry 7). In contrast to aromatic amines, the formation of diazene **6** by in situ oxidation for **3h** was not observed.[12]

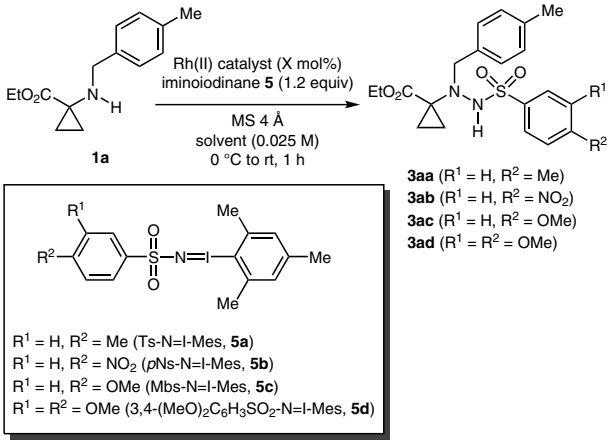


Scheme 1 (a) Rh(II)-catalyzed synthesis of *N*-aryl-*N′*-tosyldiazenes from aromatic primary amines. (b) Rh(II)-catalyzed N–H amination of aliphatic amines; esp = α,α,α,α-tetramethyl-1,3-benzenedipropanoate, Ts = tosyl, Mes = 2,4,6-trimethylphenyl.

Cyclic α-amino acid derivatives **1i** and **1j** bearing cyclobutene and cyclopentane rings underwent N–H amination as well as 1-aminocyclopropanecarboxylates, and **3i** and **3j** were obtained in 86% and 85% yields, respectively (Scheme 2). A high yield was maintained with acyclic substrate **1k**. Notably, common α-amino acid derivatives, such as alanine **1l**, tyrosine **1m**, and glycine **1n**, were also suitable substrates for this transformation, and α-hydrazino acids **3l–n** were obtained in 71–79% yields. In contrast, proline methyl ester (**1o**) failed to give the desired product **3o**.

The reactions of amines other than α-amino acids were also examined (Scheme 3). Unfortunately, dibenzylamine (**2a**) did not provide the desired N–H insertion product **4a**. However, the introduction of one or two methyl groups into

Table 1 Optimization of Reaction Conditions for N–H Amination of 1-Aminocyclopropanecarboxylate **1a**[a]



Entry	Rh(II) catalyst (loading mol%)	Iminoiodinane	Solvent	Yield (%)[b]
1	$Rh_2(HNCOCF_3)_4$ (4)	**5a**	CH_2Cl_2	**3aa** 51
2	$Rh_2(HNCOCF_3)_4$ (4)	**5b**	CH_2Cl_2	**3ab** 30
3	$Rh_2(HNCOCF_3)_4$ (4)	**5c**	CH_2Cl_2	**3ac** 84
4	$Rh_2(HNCOCF_3)_4$ (4)	**5d**	CH_2Cl_2	**3ad** 88
5	$Rh_2(HNCOCF_3)_4$ (2)	**5d**	CH_2Cl_2	**3ad** 92
6	$Rh_2(esp)_2$ (2)	**5d**	CH_2Cl_2	**3ad** 89
7	$Rh_2(esp)_2$ (2)	**5d**	CH_2Cl_2[c]	**3ad** 71
8	$Rh_2(esp)_2$ (2)	**5d**	MeCN	**3ad** 23
9	$Rh_2(esp)_2$ (2)	**5d**	Et_2O	**3ad** 67
10	$Rh_2(esp)_2$ (2)	**5d**	toluene	**3ad** 88
11	$Rh_2(esp)_2$ (2)	**5d**	$CF_3C_6H_5$	**3ad** 94 (81)[d]

[a] Reaction conditions: **1a** (0.10 mmol), Rh(II) catalyst (2–4 mol%), iminoiodinane (0.20 mmol), and MS 4 Å (powder, 40 mg) in the indicated solvent (4.0 mL).
[b] Isolated yields.
[c] Concentration: 0.1 M.
[d] Yield in parenthesis refers to the yield obtained in 1 mmol scale; Ts = tosyl, *p*Ns = *p*-nosyl, Mbs = 4-methoxyphenylsulfonyl.

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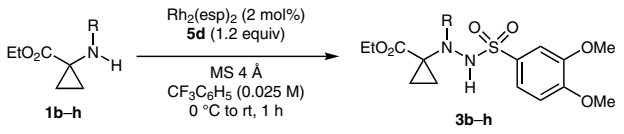
the α-position of **2a** significantly improved the outcomes, and **4b** and **4c** were obtained in 54% and 58% yields, respectively. It was speculated that this noticeable difference between **2a** and **2b**,**c** was due to catalyst poisoning by the highly nucleophilic **2a**.[11]

To validate this hypothesis, the N–H amination of **1a** in the presence of **2a** was performed (Table 3). The addition of only 0.2 equiv of **2a** led to a decrease in the yield of **3ad** from 94% (Table 1, entry 11) to 36%, along with a 30% recovery of the starting **1a**. Furthermore, the quantitative amount of **2a** completely inhibited the reaction of **1a**. Conversely, with 20 mol% of $Rh_2(esp)_2$, the N–H amination of **1a** proceeded even in the presence of a quantitative amount of **2a**. These results clearly indicate catalyst poisoning by **2a**. A plausible reaction mechanism is illustrated in Scheme 4. With amino acid derivatives **1** or bulky amines **2b**,**c**, Rh(II)–nitrene species generated from $Rh_2(esp)_2$ and iminoiodinane **5d** undergo nucleophilic addition of the substrates to form N–N bonds. Proton transfer from intermediate **I** furnishes N–H amination products **3** or **4**. Meanwhile, **2a** interferes with the generation of Rh(II)–nitrene through the formation of an inactive complex by coordination with $Rh_2(esp)_2$.

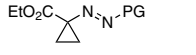
In summary, we developed a Rh(II)-catalyzed N–N bond-forming reaction of amino acid derivatives or aliphatic amines to provide hydrazine derivatives through the

Table 2 N–H Amination of *N*-Alkyl-1-aminocyclopropanecarboxylates **1b–h**

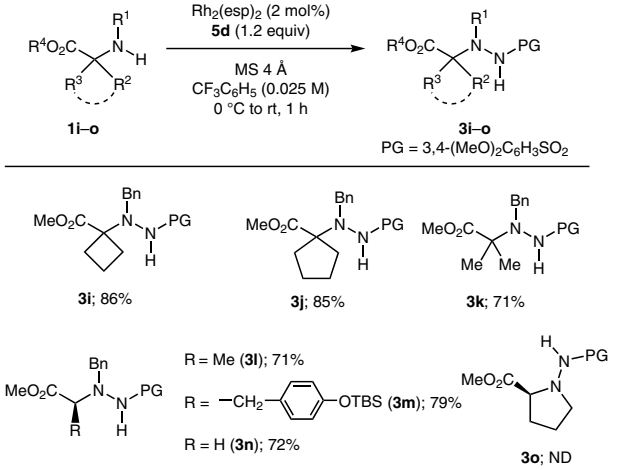


Entry	R	Yield (%)[a]
1	4-$MeOC_6H_4CH_2$	**3b** 90
2	4-$O_2NC_6H_4CH_2$	**3c** 87
3	4-$BrC_6H_4CH_2$	**3d** 95
4	2-$BrC_6H_4CH_2$	**3e** 85
5	allyl	**3f** 86
6	*i*-Pr	**3g** 59
7	H	**3h** 47[b]

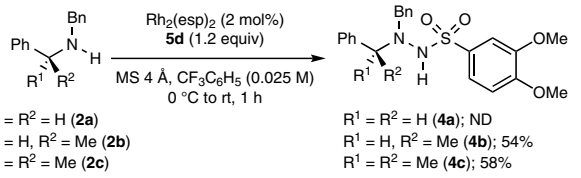
[a] Isolated yield.
[b] Diazene **6** was not obtained.



6 [PG = 3,4-$(MeO)_2C_6H_3SO_2$]

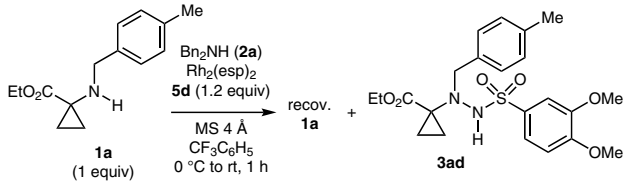


Scheme 2 N–H Amination of amino acid derivatives **1i–o**; TBS = *tert*-butyldimethylsilyl



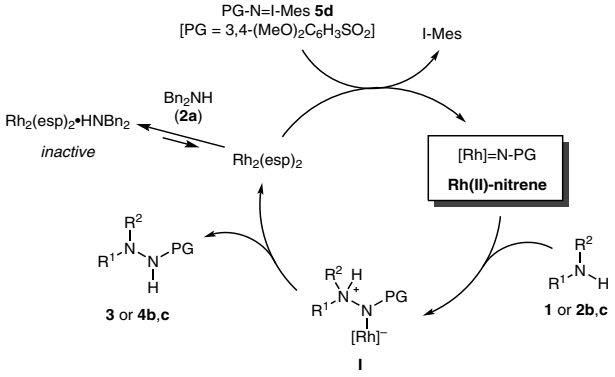
Scheme 3 N–H Amination of aliphatic amines **2a–c**

Table 3 N–H Amination of **1a** in the Presence of Dibenzylamine (**2a**)



Entry	**2a** (equiv)	$Rh_2(esp)_2$ (mol%)	Recovered **1a** (%)[a]	Yield of **3ad** (%)[a]
1	0.2	2	30	36
2	1	2	81	ND
3	1	20	31	47

[a] Isolated yield.



Scheme 4 Plausible reaction mechanism

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combined use of $Rh_2(esp)_2$ and iminoiodinane bearing (3,4-dimethoxyphenyl)sulfonyl group on the nitrogen atom. This is the first report of N–H amination of aliphatic amines with metal–nitrene species. Further studies on the influence of the arylsulfonyl group on the reactivity of Rh(II)–nitrene and the removal of (3,4-dimethoxyphenyl)sulfonyl group are currently in progress.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0041-1737759.

References and Notes

(1) (a) Blair, L. M.; Sperry, J. *J. Nat. Prod.* **2013**, *76*, 794. (b) Oelke, A. J.; France, D. J.; Hofmann, T.; Wuitschik, G.; Ley, S. V. *Nat. Prod. Rep.* **2011**, *28*, 1445. (c) Dean, C.; Rajkumar, S.; Roesner, S.; Carson, N.; Clarkson, G. J.; Wills, M.; Jones, M.; Shipman, M. *Chem. Sci.* **2020**, *11*, 1636.

(2) (a) Kang, C. W.; Sarnowski, M. P.; Elbatrawi, Y. M.; Del Valle, J. R. *J. Org. Chem.* **2017**, *82*, 1833. (b) Rathman, B. M.; Allen, J. L.; Shaw, L. N.; Del Valle, J. R. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 127283.

(3) (a) Ragnarsson, U. *Chem. Soc. Rev.* **2001**, *30*, 205. (b) Guo, Q.; Lu, Z. *Synthesis* **2017**, *49*, 3835.

(4) (a) Vidal, J.; Hannachi, J.-C.; Hourdin, G.; Mulatier, J.-C.; Collet, A. *Tetrahedron Lett.* **1998**, *39*, 8845. (b) Armstrong, A.; Jones, L. H.; Knight, J. D.; Kelsey, R. D. *Org. Lett.* **2005**, *7*, 713.

(5) (a) Rosen, B. R.; Werner, E. W.; O'Brien, A. G.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5571. (b) Ryan, M. C.; Martinelli, J. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2018**, *140*, 9074. (c) Yin, D.; Jin, J. *Eur. J. Org. Chem.* **2019**, 5646. (d) Vemuri, P. Y.; Patureau, F. W. *Org. Lett.* **2021**, *23*, 3902.

(6) Reviews, see: (a) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (b) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911. (c) Buendia, J.; Grelier, G.; Dauban, P. *Adv. Organomet. Chem.* **2015**, *64*, 77. (d) Darses, B.; Rodrigues, R.; Neuville, L.; Mazurais, M.; Dauban, P. *Chem. Commun.* **2017**, *53*, 493. (e) Hayashi, H.; Uchida, T. *Eur. J. Org. Chem.* **2020**, 909. (f) Vine, L. E.; Zerull, E. E.; Schomaker, J. M. *Synlett* **2021**, *32*, 30. (g) Rodríguez, M. R.; Díaz-Requejo, M. M.; Pérez, P. J. *Synlett* **2021**, *32*, 763. (h) Wang, Y.-C.; Lai, X.-J.; Huang, K.; Yadav, S.; Qiu, G.; Zhang, L.; Zhou, H. *Org. Chem. Front.* **2021**, *8*, 1677.

(7) (a) Jain, S. L.; Sharma, V. B.; Sain, B. *Tetrahedron Lett.* **2003**, *44*, 4385. (b) Li, J.; Cisar, J. S.; Zhou, C.-Y.; Vera, B.; Williams, H.; Rodríguez, A. D.; Cravatt, B. F.; Romo, D. *Nat. Chem.* **2013**, *5*, 510. (c) Maestre, L.; Dorel, R.; Pablo, Ó.; Escofet, I.; Sameera, W. M. C.; Álvarez, E.; Maseras, F.; Díaz-Requejo, M. M.; Echavarren, A. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2017**, *139*, 2216.

(8) It is reported that aminimides formed through the reactions of bicyclic aminals or (sulfon)amides and Rh(II)–nitrene underwent rearrangement to form formal C–N or S–N bond insertion products: (a) Pujari, S. A.; Guénée, L.; Lacour, J. *Org. Lett.* **2013**, *15*, 3930. (b) Kono, M.; Harada, S.; Nemoto, T. *Chem. Eur. J.* **2019**, *25*, 3119.

(9) We previously reported *ortho* C–H amination of tertiary aromatic amines with Rh(II)–nitrene and presumed that the regioselectivity was due to the interaction between amino group and nitrogen atom of Rh(II)-nitrene: (a) Ito, M.; Nakagawa, T.; Higuchi, K.; Sugiyama, S. *Org. Biomol. Chem.* **2018**, *16*, 6876. (b) Ito, M.; Mori, M.; Nakagawa, T.; Hori, M.; Higuchi, K.; Sugiyama, S. *Heterocycles* **2021**, *103*, 403.

(10) Wang, H.; Jung, H.; Song, F.; Zhu, S.; Bai, Z.; Chen, D.; He, G.; Chang, S.; Chen, G. *Nat. Chem.* **2021**, *13*, 378.

(11) (a) Yang, M.; Wang, X.; Li, H.; Livant, P. *J. Org. Chem.* **2001**, *66*, 6729. (b) Li, M.-L.; Yu, J.-H.; Li, Y.-H.; Zhu, S.-F.; Zhou, Q.-L. *Science* **2019**, *366*, 990. (c) Shinohara, H.; Saito, H.; Homma, H.; Mizuta, K.; Miyairi, S.; Uchiyama, T. *Tetrahedron* **2020**, *76*, 131619.

(12) (a) Ito, M.; Tanaka, A.; Higuchi, K.; Sugiyama, S. *Eur. J. Org. Chem.* **2017**, 1272. An example of hydrazine formation from *N*-allylaniline is also reported in this study: (b) Ito, M.; Tanaka, A.; Hatakeyama, K.; Kano, E.; Higuchi, K.; Sugiyama, S. *Org. Chem. Front.* **2020**, *7*, 64.

(13) *N*-Benzyl-1-aminocyclopropanecarboxylate provided a similar result to **1a**. We choose **1a** as the substrate because purification of the N–H amination product **3ad** was easier than that obtained from the *N*-benzyl substrate.

(14) In our previous work, the reaction at higher concentration (0.1 M) led to the formation of azo compounds by dimerization of primary aromatic amines, see ref. 12a.

(15) **Typical Experimental Procedure**
3,4-$(MeO)_2C_6H_3SO_2N$=IMes (**5d**, 554 mg, 1.20 mmol) was added to a stirred mixture of **1a** (233 mg, 1.00 mmol), $Rh_2(esp)_2$ (15.2 mg, $2.00\cdot10^{-2}$ mmol, 2 mol%), and MS 4 Å (powder, 400 mg) in $CF_3C_6H_5$ (40 mL) at 0 °C under Ar atmosphere. After stirring at room temperature for 1 h, the whole mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to furnish the crude product, which was purified by column chromatography (silica gel, 1:1 *n*-hexane/AcOEt) to give **3ad** (364 mg, 81%) as orange oil. IR (KBr): ν = 3279, 2933, 1722, 1511, 1165, 1029 cm^{-1}. ^1H NMR (400 MHz, CD_3CN, 60 °C): δ = 0.90 (br d, 2 H, *c*-propane), 1.05 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.25 (br s, 2 H, *c*-propane), 2.21 (s, 3 H, $ArCH_3$), 3.66 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 3.90 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.41 (s, 2 H, $ArCH_2$), 6.60 (dd, *J* = 8.4, 2.6 Hz, 1 H, ArH), 6.62 (d, *J* = 2.6 Hz, 1 H, ArH), 6.77 (d, *J* = 8.4 Hz, 1 H, ArH), 7.02 (d, *J* = 8.0 Hz, 2 H, ArH), 7.09–7.11 (m, 3 H, NH and ArH). ^{13}C NMR (100 MHz, CD_3CN, 60 °C): δ = 14.6 (CH_3), 20.1 (CH_2), 21.3 (CH_3), 43.6 (C), 54.8 (CH_2), 56.9 (CH_3), 57.2 (CH_3), 62.5 (CH_2), 109.9 (CH), 113.9 (CH), 116.8 (CH), 130.1 (CH), 130.5 (CH) 131.9 (C), 135.2 (C), 138.8 (C), 148.8 (C), 151.0 (C), 174.0 (C=O). HRMS (EI): *m/z* calcd for $C_{22}H_{28}N_2O_6S$ $[M]^+$: 448.1668; found: 448.1666.

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