

HETEROCYCLES, Vol. 86, No. 2, 2012, pp. 933 - 940. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 30th June, 2012, Accepted, 16th August, 2012, Published online, 23rd August, 2012
DOI: 10.3987/COM-12-S(N)77

A NOVEL THREE-COMPONENT COUPLING REACTION OF ARYNES, ISOCYANIDES, AND CYANOFORMATES: A STRAIGHTFORWARD ACCESS TO CYANO-SUBSTITUTED IMINOISOBENZOFURANS

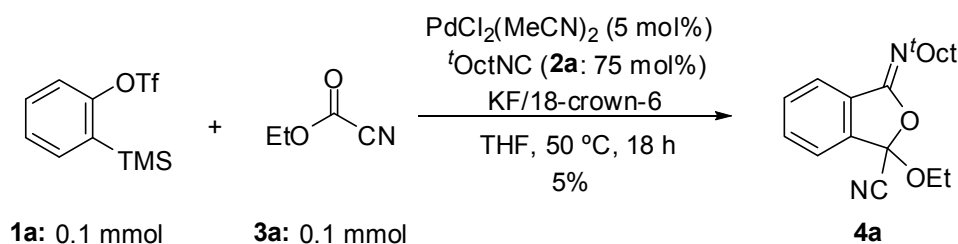
Jing Li,¹ Shintaro Noyori,¹ Masayuki Iwasaki,¹ Kiyohiko Nakajima,² and Yasushi Nishihara^{1*}

Division of Earth, Life, and Molecular Sciences, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushimanaka, Kita-ku, Okayama 700-8530, Japan. Department of Chemistry, Aichi University of Education, Igaya, Kariya 448-8542, Japan. E-mail: ynishiha@okayama-u.ac.jp

Abstract – Iminoisobenzofuran derivatives have been prepared in moderate yields by the palladium-catalyzed three-component coupling reaction of arynes, isocyanides, and cyanofurans.

This paper is dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday.

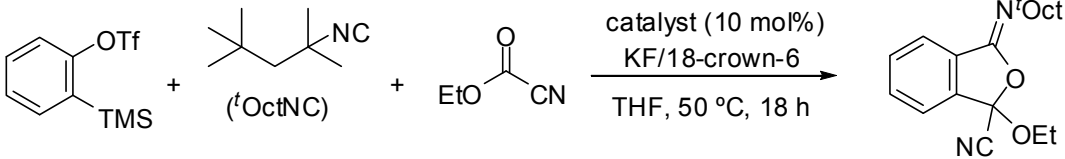
Arynes are versatile and useful tools in synthetic organic chemistry, notably for the construction of multi-substituted arenes which are hard to access by conventional methods.¹ We have reported the palladium-catalyzed cyanoesterification of norbornene derivatives via carbon-carbon bond cleavage of cyanofurans.² In the course of our attempts to find a new route for cyanoesterification of benzyne, a benzyne precursor, 2-(trimethylsilyl)phenyl triflate (**1a**), was treated with a fluoride ion (KF/18-crown-6)³ in conjunction with a palladium catalyst and 1,1,3,3-tetramethylbutyl isocyanide (**2a**: ^tOctNC) as a ligand. Using this system as an approach to ethyl 2-cyanobenzoate by using ethyl cyanofurane (**3a**), we observed that *N*-[3-cyano-3-ethoxy-1(3*H*)-isobenzofuranylidene]-2,4,4-trimethyl-2-pentanamine (**4a**) was formed as a minor byproduct in 5% yield (Scheme 1). Independent studies by the groups of Yoshida and Kunai (aldehydes, ketones, and sulfonylimines)⁴ and Stoltz (phenyl esters)⁵ in the three-component coupling reactions of arynes with isocyanides provided the direct synthesis of benzoannulated iminofurans.⁶ Herein we disclose the use of a variety of cyanofurans as the third coupling partners in such three-component assemblies with arynes and isocyanides, affording five-membered iminoisobenzofuran derivatives with structural diversity.



Scheme 1. Palladium-Catalyzed Three-Component Coupling.

As seen in Table 1, a variety of catalysts and solvents were exploited to improve the product yield of **4a**. We began our study on the three-component coupling by using **1a**, **2a**, and **3a** in the presence of potassium fluoride/18-crown-6 in THF without transition metal catalyst at 50 °C for 18 h. However, none of the desired product **4a** was formed (entry 1). This result is in contrast to the results obtained by Yoshida and Kunai,⁴ and Stoltz,⁵ in which iminoisobenzofuran derivatives were synthesized by adding only a fluoride ion (KF or TBAT) in the three-component coupling reactions. When $\text{PdCl}_2(\text{PhCN})_2$ was added as the catalyst, the formation of product **4a** was observed in 56% GC yield (entry 2). Initial screening for prospective catalysts revealed that various Pd and Rh catalysts such as $[\text{Pd}(\eta\text{-C}_3\text{H}_5)(\text{cod})]\text{BF}_4$,⁷ $[\text{Rh}(\text{cod})_2]\text{BF}_4$,⁸ $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{PF}_6)_2$,⁹ or $[\text{Cp}^*\text{RhCl}_2]_2$,¹⁰ could catalyze this reaction to some extent (entries 3-6). Further investigation has shown that the 68% GC yield of the product **4a** was obtained when $[\text{Pd}(\text{PhCN})_2(\text{dppf})](\text{BF}_4)_2$ ¹¹ was employed as the catalyst (entry 7). We investigated to use other solvents such as *n*-butyl ether or benzonitrile (entries 8 and 9), however, lower yields were generally observed and the reaction would not proceed at all in 1,4-dioxane (entry 10). Finally, we defined the optimized ratios of the substrates as the standard conditions: 2 equiv of benzyne precursor **1a** and isocyanide **2a** to **3a** in the presence of 4 equiv of KF/18-crown-6 under 10 mol% of $[\text{Pd}(\text{PhCN})_2(\text{dppf})](\text{BF}_4)_2$. To the best of our knowledge, this synthetic method provides the first example of an alkoxy- and cyano-substituted iminoisobenzofuran.

Under the optimized reaction conditions, we then employed a variety of isocyanides **2** and cyanoformates **3** in order to examine the scope of this transformation. As described in Table 2, the three-component coupling reactions proceeded smoothly to form the corresponding cyano-substituted iminoisobenzofurans **4**. The reactions of cyanoformates **3b-3f** bearing different substituents efficiently occurred to give the desired products **4b-4f** in good yields (entries 2-6).¹² The structure of **4a** was unambiguously confirmed through careful NMR spectroscopy, MS, and X-ray diffraction analysis. As shown in Figure 1, the imine moiety in the product **4a** was found to have the *Z* configuration.¹³

Table 1. Three-Component Coupling of Benzyne Precursor **1a**, 1,1,3,3-Tetramethylbutyl Isocyanide (**2a**) and Ethyl Cyanoformate (**3a**).^a


entry	catalyst	solvent	yield (%) ^b
1	none	THF	0
2	PdCl ₂ (PhCN) ₂	THF	56
3	[Pd(η -C ₃ H ₅)(cod)]BF ₄	THF	52
4	[Rh(cod) ₂]BF ₄	THF	45
5	[Cp*Rh(MeCN) ₃](PF ₆) ₂	THF	47
6	[Cp*RhCl ₂] ₂	THF	16
7	[Pd(PhCN) ₂ (dppf)](BF ₄) ₂	THF	68 (44) ^c
8	[Pd(PhCN) ₂ (dppf)](BF ₄) ₂	ⁿ Bu ₂ O	31
9	[Pd(PhCN) ₂ (dppf)](BF ₄) ₂	PhCN	24
10	[Pd(PhCN) ₂ (dppf)](BF ₄) ₂	1,4-dioxane	0

^aThe reaction was carried out using **1a** (0.15 mmol), **2a** (0.15 mmol), **3a** (0.075 mmol), KF (0.3 mmol), 18-crown-6 (0.3 mmol), and a catalyst (10 mol%) in a solvent (0.5 mL) at 50 °C for 18 h. ^bYields were determined by GC using tetradecane as an internal standard, based on cyanoformate **3a**. ^cAn isolated yield. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

In the case of the aromatic cyanoformate **3g**, the desired product **4g** was not generated because the cationic Pd catalyst gave diphenyl carbonate as a by-product (entry 7). Except for **2a**, the aliphatic substituted isocyanides such as *tert*-butyl isocyanide (**2b**) participated in the three-component coupling reaction to afford **4h** in 42% (entry 8). In all cases, the unidentified by-products showed the same molecular weight as **4**, indicating structural isomers; these products were observed by GC-MS.

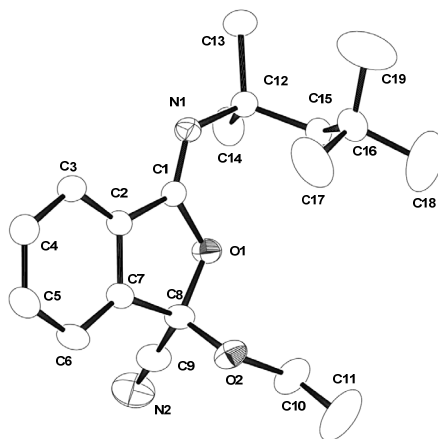
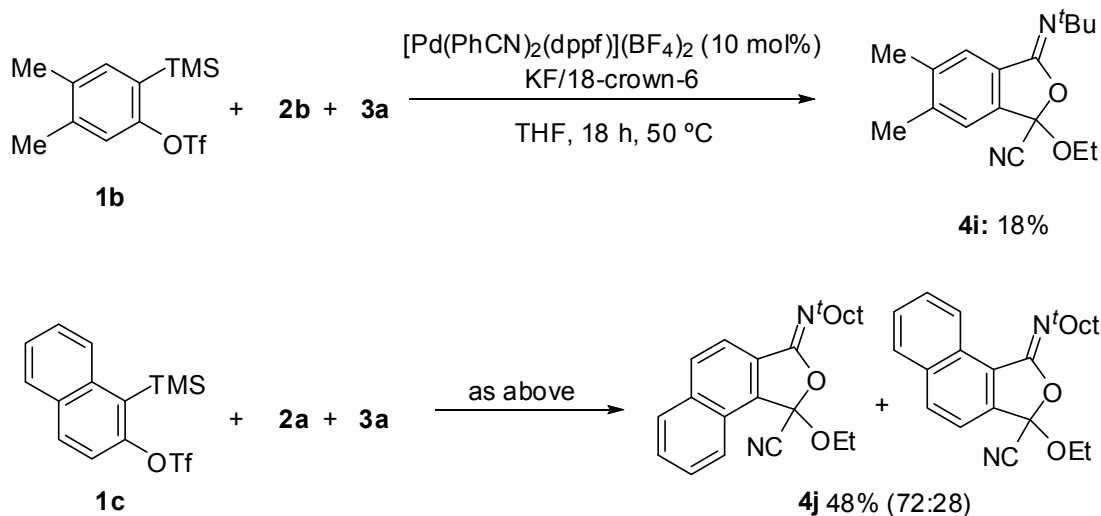
**Figure 1.** Structure of complex **4a** determined by X-ray crystallography with 30% thermal ellipsoidal plotting. Hydrogen atoms are omitted for simplicity.

Table 2. Pd-Catalyzed Three-Component Coupling of **1a**, Isocyanides **2**, and Cyanoformates **3**.^a

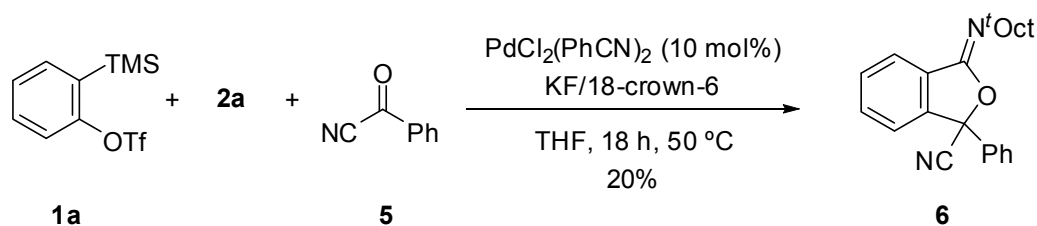
entry	isocyanide (R ¹ =)	cyanoformates (R ² =)	product	yield (%) ^b
1	CMe ₂ CH ₂ ^t Bu (^t Oct) (2a)	OEt (3a)	4a	44
2	2a	OMe (3b)	4b	47
3	2a	O ⁿ Pr (3c)	4c	44
4	2a	O ⁱ Pr (3d)	4d	46
5	2a	O ⁿ Bu (3e)	4e	40
6	2a	OBn (3f)	4f	51
7	2a	OPh (3g)	4g	0
8	^t Bu (2b)	3a	4h	42

^a The reactions were carried out using **1a** (1 mmol), **2** (1 mmol), **3** (0.5 mmol), KF (2 mmol) and 18-crown-6 (2 mmol), Pd catalyst (10 mol%) in THF (3.3 mL) at 50 °C for 18 h. ^b Isolated yields, based on cyanoformate **3**.

To understand the effect of substituents on the benzyne moiety in the present reaction, substituted benzyne precursors **1b** and **1c** were tested (Scheme 2). Under the optimized reaction conditions, compound **1b**, containing 4,5-dimethyl substitution, reacted smoothly with **2b** and **3a** to give the three-component coupled product **4i** in 18% yield. When 1-(trimethylsilyl)naphth-2-yl triflate (**1c**) was subjected to the reaction, a 72:28 mixture of isomers **4j** was obtained in 48% combined yield. We presume that the major product was formed by the attack of the isocyanide on the 2-position due to the steric congestion.^{4b}

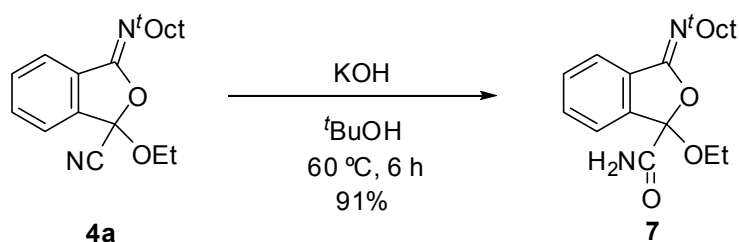
**Scheme 2.** Three-Component Coupling with Arynes (**1b** and **1c**).

The reaction was also found to be applicable to benzoyl cyanide (**5**). As shown in Scheme 3, benzoyl cyanide (**5**) reacted with **1a** and **2a** to afford product **6** in 20% yield.



Scheme 3. Three-Component Coupling of Benzyne, Benzoyl Cyanide, and 1,1,3,3-Tetramethylbutyl Isocyanide.

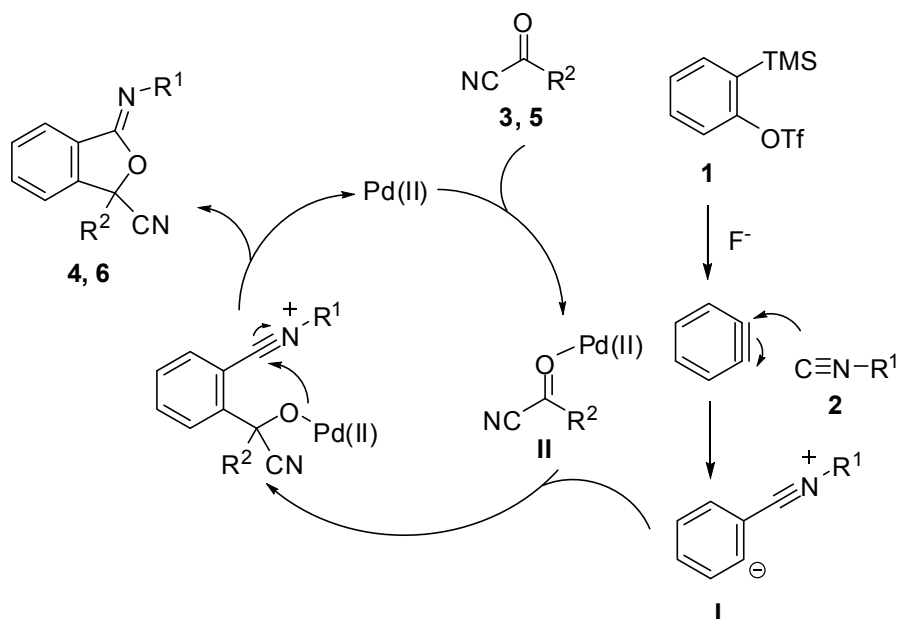
The desired final products **4** can be used as intermediates to generate products containing functionality via further reaction with the cyano group. A simple transformation for an amide prepared by the treatment of **4a** with potassium hydroxide to form **7** in 91% yield, while leaving the C=N bond intact, is shown in Scheme 4.



Scheme 4. Transformation of **4a** into the Corresponding Amide **7**.

Arynes are known to exhibit high electrophilic character, and even neutral nucleophiles readily add to arynes to produce zwitterions, which act as key intermediates in the construction of complex organic molecules.¹⁴ Thus the use of a suitable combination of nucleophiles and electrophiles allows arynes to serve as connectors between these two components, leading to a variety of three-component coupling reactions of high synthetic significance.¹⁵ We propose a mechanism for this reaction which is presented in Scheme 4. First, the nucleophilic attack of the carbon atom of isocyanide **2** to the aryne, formed from **1** occurs to generate zwitterions **I**. Meanwhile, a cationic palladium(II) complex activates cyanoformates **3** (or benzoyl cyanide (**5**)). The resulting zwitterions **I** then adds to the cyanoformate activated by cationic palladium species **II**, and a subsequent intramolecular cyclization affords the product **4** (or **6**). Because the amides derived from the protonation of **I** were observed in some cases, the reaction between **I** and **II** would be the rate-determining step. We suspect that the added cationic palladium catalyst might have an interaction with **3** or **5** to increase their electrophilicity. However,

other Lewis acids such as BPh_3 and $\text{BF}_3 \cdot \text{OEt}_2$ did not promote the reaction, resulting in the recovered starting materials.



Scheme 4. A Plausible Reaction Pathway of the Palladium-Catalyzed Three-Component Coupling.

In conclusion, we have demonstrated that arynes can be utilized in a three-component coupling reaction with a suitable combination of isocyanides and cyanoformate to produce iminoisobenzofuran derivatives. Further studies on the new three-component coupling via carbon-carbon bond cleavage of cyanoformates using arynes are now in progress.

ACKNOWLEDGEMENTS

This work was partially supported by a Grant-in-Aid for Scientific Research (KAKENHI) (No. 24550119) from JSPS. The authors gratefully thank Ms. Megumi Kosaka and Mr. Motonari Kobayashi at the Department of Instrumental Analysis, Advanced Science Research Center, Okayama University for the measurements of elemental analyses and the SC-NMR Laboratory of Okayama University for the NMR spectral measurements.

REFERENCES

1. (a) R. W. Hoffmann, *Dehydrobenzene and Cycloalkynes*, Academic Press, New York, 1967; (b) H. Hart, *The Chemistry of Triple-Bonded Functional Groups, Supplement C2* (ed. by S. Patai), Wiley, Chichester, 1994, chap. 18; (c) H. Pellissier and M. Santelli, *Tetrahedron*, 2003, **59**, 701; (d) H. H. Wenk, M. Winkler, and W. Sander, *Angew. Chem. Int. Ed.*, 2003, **42**, 502; (e) D. Peña, D. Pérez, and

- E. Guitián, *Angew. Chem. Int. Ed.*, 2006, **45**, 3579; (f) S. S. Bhojgude and A. T. Biju, *Angew. Chem. Int. Ed.*, 2012, **51**, 1520; (g) F. Sha, L. Wu, and X. Huang, *J. Org. Chem.*, 2012, **77**, 3754.
- (a) Y. Nishihara, Y. Inoue, M. Itazaki, and K. Takagi, *Org. Lett.*, 2005, **7**, 2639; (b) Y. Nishihara, Y. Inoue, S. Izawa, M. Miyasaka, K. Tanemura, K. Nakajima, and K. Takagi, *Tetrahedron*, 2006, **62**, 9872; (c) Y. Nishihara, M. Miyasaka, Y. Inoue, T. Yamaguchi, M. Kojima, and K. Takagi, *Organometallics*, 2007, **26**, 4054.
 - Y. Himeshima, T. Sonoda, and H. Kobayashi, *Chem. Lett.*, 1983, 1211.
 - (a) H. Yoshida, H. Fukushima, J. Ohshita, and A. Kunai, *Angew. Chem. Int. Ed.*, 2004, **43**, 3935; (b) H. Yoshida, H. Fukushima, T. Morishita, J. Ohshita, and A. Kunai, *Tetrahedron*, 2007, **63**, 4793; (c) H. Yoshida and K. Takaki, *Heterocycles*, 2012, **85**, 1333.
 - K. M. Allan, C. D. Gilmore, and B. M. Stoltz, *Angew. Chem. Int. Ed.*, 2011, **50**, 4488.
 - (a) Y. Ito, H. Kato, and T. Saegusa, *J. Org. Chem.*, 1982, **47**, 741; (b) A. I. Meyers, M. A. Hanagan, L. M. Trefonas, and R. J. Baker, *Tetrahedron*, 1983, **39**, 1991; (c) V. Nair and A. U. Vinod, *Chem. Commun.*, 2000, 1019; (d) A. Fayol and J. Zhu, *Angew. Chem. Int. Ed.*, 2002, **41**, 3633; (e) N. Chatani, M. Oshita, M. Tobisu, Y. Ishii, and S. Murai, *J. Am. Chem. Soc.*, 2003, **125**, 7812; (f) A. Fayol and J. Zhu, *Org. Lett.*, 2004, **6**, 115; (g) A. V. Lygin and A. de Meijere, *J. Org. Chem.*, 2009, **74**, 4554; (h) K. Kobayashi, S. Fujita, D. Nakai, S. Fukumoto, S. Fukamachi, and H. Konishi, *Helv. Chim. Acta*, 2010, **93**, 1274; (i) K. Kobayashi, Y. Shirai, S. Fukamachi, and H. Konishi, *Synthesis*, 2010, 666; (j) Z.-Y. Yan, C.-M. Tan, X. Wang, F. Li, G.-L. Gao, X.-M. Chen, W.-S. Wu, and J.-J. Wang, *Synlett*, 2011, 1863; (k) D. Chen, G.-Y. Song, A. Jia, and X.-W. Li, *J. Org. Chem.*, 2011, **76**, 8488; (l) K. Kobayashi, K. Matsumoto, and H. Konishi, *Heterocycles*, 2011, **83**, 99.
 - G. Carturan, M. Biasiolo, S. Daniele, G. A. Mazzocchin, and P. Ugo, *Inorg. Chim. Acta*, 1986, **119**, 19.
 - H.-B. Qiu, Y. Inoue, and S.-N. Che, *Angew. Chem. Int. Ed.*, 2009, **48**, 3069.
 - T. Hirakawa, K. Ikeda, H. Ogasa, M. Kawatsura, and T. Itoh, *Synlett*, 2010, 2887.
 - Y. Du, T. K. Hyster, and T. Rovis, *Chem. Commun.*, 2011, **47**, 12074.
 - S. Oi, K. Kashiwagi, E. Terada, K. Ohuchi, and Y. Inoue, *Tetrahedron Lett.*, 1996, **37**, 6351.
 - Typical procedure for the synthesis of cyano-substituted iminoisobenzofurans by three-component coupling reactions (Table 2, entry 1).** A flame-dried 25 mL Schlenk tube with a magnetic stir bar was charged with KF (116 mg, 2.0 mmol), 18-crown-6 (529 mg, 2.0 mmol), and [Pd(PhCN)₂(dppf)](BF₄)₂ (52 mg, 0.05 mmol, 10 mol%) in THF (3.3 mL) under argon. To this solution were added 2-(trimethylsilyl)phenyl triflate (**1a**) (243 μL, 1.0 mmol), *t*-octylisocyanide (**2a**) (175 μL, 1.0 mmol), and ethyl cyanofomate (**3a**) (49 μL, 0.5 mmol) sequentially via syringe. The reaction mixture was heated to 50 °C for 18 h, then cooled to ambient temperature, quenched with

water, and extracted with Et₂O (20 mL × 3). The combined extracts were washed with brine and dried over anhydrous sodium sulfate. The volatiles were removed under reduced pressure to give crude product, which was purified by silica gel column chromatography (eluent: hexane/EtOAc, 19:1). Further purification with HPLC (eluent: CHCl₃) gave *N*-[3-cyano-3-ethoxy-1(3*H*)-isobenzofuranylidene]-2,4,4-trimethyl-2-pentanamine (**4a**) (69 mg, 0.22 mmol, 44%) as yellow solid. ¹H NMR (300 MHz, CDCl₃, rt): δ 1.01 (s, 9H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.46 (s, 6H), 1.76 (d, *J* = 2.4 Hz, 2H), 4.01 (m, 2H), 7.55-7.62 (m, 3H), 7.76-7.79 (m, 1H); ¹³C NMR (75 MHz, CDCl₃, rt): δ 14.9, 30.4, 30.5, 31.7, 32.0, 55.3, 58.4, 63.6, 98.8, 114.8, 122.5 (× 2), 123.9, 131.7, 132.1, 139.2, 147.6. IR (KBr, cm⁻¹): 2239 (w, C≡N), 1715 (s, C=N). MS (EI, *m/z* (relative intensity)): 314 (M⁺, 2), 299 (71), 253 (28), 243 (86), 197 (54), 159 (31), 158 (100), 157 (67), 148 (31), 130 (71), 102 (43). Anal. Calc for C₁₉H₂₆N₂O₂: C 72.58; H 8.33; N 8.91. Found: C 72.22; H 8.42; N 8.75.

13. Crystallographic data for the structure of **4a** have been deposited with The Cambridge Crystallographic Data Centre as the deposition number CCDC 886033. This data can be obtained free of charge from on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or www.ccdc.cam.ac.uk/data_request/cif].
14. (a) S. V. Kessar, *Comprehensive Organic Synthesis*, Vol. 4 (ed. by B. M. Trost and I. Fleming), Pergamon, Oxford, 1991, pp. 483-515; (b) E. R. Biehl and S. P. Khanapure, *Acc. Chem. Res.*, 1989, **22**, 275.
15. (a) E. Yoshikawa and Y. Yamamoto, *Angew. Chem. Int. Ed.*, 2000, **39**, 173; (b) N. Chatani, A. Kamitani, M. Oshita, Y. Fukumoto, and S. Murai, *J. Am. Chem. Soc.*, 2001, **123**, 12686; (c) H. Yoshida, H. Fukushima, J. Ohshita, and A. Kunai, *Tetrahedron Lett.*, 2004, **45**, 8659; (d) T. T. Jayanth, M. Jeganmohan, and C.-H. Cheng, *Org. Lett.*, 2005, **7**, 2921; (e) J. L. Henderson, A. S. Edwards, and M. F. Greaney, *J. Am. Chem. Soc.*, 2006, **128**, 7426; (f) M. Jeganmohan and C.-H. Cheng, *Chem. Commun.*, 2006, 2454; (g) H. Yoshida, H. Fukushima, J. Ohshita, and A. Kunai, *J. Am. Chem. Soc.*, 2006, **128**, 11040; (h) I. Larrosa, M. I. Da Silva, P. M. Gómez, P. Hannen, E. Ko, S. R. Lenger, S. R. Linke, A. J. P. White, D. Wilton, and A. G. M. Barrett, *J. Am. Chem. Soc.*, 2006, **128**, 14042; (i) F. Sha and X. Huang, *Angew. Chem. Int. Ed.*, 2009, **48**, 3458; (j) E. Yoshioka, S. Kohtani, and H. Miyabe, *Angew. Chem. Int. Ed.*, 2011, **50**, 6638.