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General and Efficient Cu-Catalyzed Three Component Coupling Reaction Toward Imidazoheterocycles: One-Pot Synthesis of Alpidem and Zolpidem**

Natalia Chernyak and **Vladimir Gevorgyan***
Department of Chemistry University of Illinois at Chicago 845 West Taylor Street, Room 4500, Chicago, IL 60607 (USA)

Imidazopyridine is an important pharmacophore widely found in many biologically active compounds.[i] Particularly, imidazo[1,2-*a*]pyridine is an essential fragment present in pharmacologically important molecules, including several anxyolytic drugs,[ii] such as alpidem (**A**),[iia,b] necopidem (**C**), and saripidem (**D**), and insomnia treatment drug zolpidem (**B**).[iic,d] Although a variety of synthetic methods for the synthesis of these important cores have been developed,[iii] most of them are limited in scope and require multistep preparation of starting materials.[iv] Accordingly, development of straightforward and general method for the synthesis of imidazo[1,2-*a*]pyridines from easily available precursors is highly warranted. Herein we wish to report general and efficient synthesis of imidazopyridines **5** via the Cu-catalyzed three component coupling (TCC) reaction of 2-aminopyridines **1** with arylaldehydes **2** and alkynes **3** (Scheme 1).

We reasoned that imidazo[1,2-*a*]pyridyl core **5** can be assembled via π-philic metal-catalyzed 5-*exo-dig* cyclization[v] of propargylamine **4**. The latter, in turn, should be accessible via three component coupling reaction of 2-aminopyridine **1**, aldehyde **2** and terminal alkyne **3** (Scheme 1).[vi] Notably, the 5-*exo-dig* cyclization **4** to **5** should secure formation of imidazo[1,2-*a*]pyridylmethyl unit, a common fragment of the mentioned above biologically important molecules[ii] (Figure 1). To test this hypothesis, we examined this reaction in the presence of different metal catalysts. Accordingly, $NaAuCl_4$, known to be efficient catalyst for the synthesis of indolizines via TCC reaction,[vii] was tested first. However, no desired product was formed under these reaction conditions (Table 1, entry 1). Our further optimizations revealed copper salts to be more efficient catalysts for this transformation. Thus, reaction in the presence of 5 mol% of $Cu(OTf)_2$ produced **5a** in 10% yield. Employment of 10 mol% of CuCl resulted in dramatic improvement of the yield (entry 3). However, reaction in the presence of 50 mol% of CuCl produced **5a** only in 74% yield. Employment of $CuCl/Cu(OTf)_2$[viii] binary catalytic system[ix] in MeCN at 100 °C provided the desired **5a** in 15 % yield. Surprisingly, the use DMA at 120 °C substantially improved the reaction outcome (entry 6). Finally, switching to less polar toluene, allowed to obtain imidazopyridine **5a** from 2-aminopyridine **1a** (1 equiv), aldehyde **2a** (1.05 equiv), and alkyne **3a** (1.5 equiv) in excellent yield (entry 7)!

Next, the generality of this novel TCC reaction has been examined (Table 2). To our delight, we found this transformation to be very general for a wide range of aldehydes and alkynes, providing an easy access to densely substituted imidazopyridines **5**. Thus, employment of

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*Fax: (+1) 312-355-0836, vlad@uic.edu, Homepage: http://www.chem.uic.edu/vggroup.

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different alkynes, bearing aryl- (entries 1, 2, 6–10, 12–22), alkyl- (entries 3–5), or silyl (entry 11) substituents, produced imidazopyridines ingood to exellent yields. Aryl- and alkyl aldehydes displayed good reactivity in this reaction, as well. A variety of functional groups at aromatic moiety of aldehyde, such as chloro- (entry 6), bromo- (entry 12), cyano- (entries 10, 13, and 18) and fluoro- (entries 14 and 15) were perfectly tolerated. Reaction with propyl- and isopropyl aldehydes occured uneventfully, furnishing C-2 alkyl substituted imidazopyridines **5g** and **5h**, respectively (entries 7 and 8). Employment of furan-2-carbaldehyde led to bishetaryl compound **5i** in 78% yield (entry 9). Formaldehyde, however, was somewhat less reactive providing monosubstituted imidazopyridine **5t** in moderate yield (entry 20). Futhermore, 2-aminoquinoline and 2-aminoisoquinoline reacted well in this transformation, affording imidazoquinoline **5u** and imidazoisoquinoline **5v** in good yields (Table 2, entries 21 and 22).

Next, we attempted synthesis of alpidem (**A**) and zolpidem (**B**) via this novel three component coupling reaction. It should be mentioned, that these drugs are synthesized via multistep procedures.[xi] We hypothesized that **A** and **B** could rapidly be accessed via the three component coupling reaction of the appropriate aminopyridine with aldehyde and corresponding propiolamide. We recognized that employment of propiolamide would pose a certain challenge, as this Michael acceptor would not be tolerated in the first step of the sequence. Thus, we performed model studies of the TCC reaction with propiolates (Scheme 2). It was found that imidazopyridines **6a-c** could be synthesized in good yields via one-pot fashion, where ethyl propyolate and copper catalysts were added to the reaction mixture upon completion of the dehydrocondensation step.

Next, one-pot synthesis of zolpidem and alpidem via the newly established protocol, employing corresponding propiolamides, was performed (Scheme 3). Gratifyingly, sequential TCC reaction of 2-amino-5-chloropyridine (**1b**) and *p*-chloroaldehyde (**2b**) with *N,N*-dipropylpropiolamide produced *alpidem* (**A**) in 83% yield. Likewise, reaction of 2-amino-5-methylpyridine (**1c**), *p*-tolualdehyde (**2c**) and *N,N*-dimethylpropiolamide gave *zolpidem* (**B**) in 72% yield.

In conclusion, we have developed general and highly efficient method for synthesis of imidazopyridines via the copper-catalyzed three component coupling reaction of aryl-, heteroaryl- and alkyl aldehydes with 2-aminopyridines and terminal alkynes. Employment of 2-aminoquinoline and 2-aminoisoquinoline as coupling partners in this transformation led to imidazoquinoline and imidazoisoquinoline cores in good yields. A synthetic utility of this novel TCC method has been illustrated in highly efficient one-pot syntheses of alpidem and zolpidem.

Experimental Section

Typical procedure for the synthesis of imidazopyridines **5a-v** via three component coupling (TCC) reaction: In a glovebox 1 mL Weaton microreactor was charged with 2-aminopyridine **1** (0.5 mmol), CuCl (2.5 mg, 0.025 mmol, 5 mol%), $Cu(OTf)_2$ (9.04 mg, 0.025 mmol, 5 mol%) (aldehyde **2**, if solid, was added at this point too). Dry toluene (500 μL, 1 M) was added under inert atmosphere, followed by aldehyde **2** (0.525 mmol, 1.05 equiv) and alkyne **3** (0.75 mmol, 1.5 equiv). The microreactor was capped with Teflon pressure cap and placed into preheated (120 °C) aluminum heating block. The reaction mixture was heated at 120°C until full consumption of 2-aminopyridine **1** (as judged by GC-MS analysis). Upon completion (12–16 h), it was filtered through a plug of neutral alumina with the aid of EtOAc. The filtrate was concentrated under reduced pressure to give crude material, which was purified by column chromatography on silica gel to give imidazopyridine **5** (eluent: Et_3N:EtOAc:Hexanes – 4:17:84).

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References

[i]. For general review on chemistry of imidazopyridines, see: Couty F, Evano G. Katritzky AR, Ramsden CA, Scriven EFV, Taylor RJK. Comprehensive Heterocyclic Chemistry III. >2008; Vol. 11OxfordElsevier:409–499. and references therein.

[ii]. For selected examples of biologically active imidazo[1,2-*a*]pyridyl derivatives, see: Okubo T, Yoshikawa R, Chaki S, Okuyamac S, Nakazato A. Bioorg. Med. Chem. 2004; 12:423. [PubMed: 14723961] Jain AN. J. Med. Chem. 2004; 47:947. [PubMed: 14761196] Harrison TS, Keating GM. CNS Drugs. 2005; 19:65. [PubMed: 15651908] Hsua N, Jha SK, Coleman T, Frank MG. Behav. Brain Res. 2009; 201:233. [PubMed: 19428639] Wiegand MH. Drugs. 2008; 68:2411. [PubMed: 19016570] Hanson SM, Morlock EV, Satyshur KA, Czajkowski C. J. Med. Chem. 2008; 51:7243. [PubMed: 18973287] Véron J-B, Allouchi H, Enguehard-Gueiffier C, Snoeck R, De Clercq GAE, Gueiffier A. Bioorg. Med. Chem. 2008; 16:9536. [PubMed: 18835175]

[iii]. For selected examples on synthesis of imidazo[1,2-*a*]pyridines, see: Fookes CJR, Pham TQ, Mattner F, Greguric I, Loc'h C, Liu X, Berghofer P, Shepherd R, Gregoire M-C, Katsifis A. J. Med. Chem. 2008; 51:3700. [PubMed: 18557607] Denora N, Laquintana V, Pisu MG, Dore R, Murru L, Latrofa A, Trapani G, Sanna E. J. Med. Chem. 2008; 51:6876. [PubMed: 18834105] Laquintana V, Denora N, Lopedota A, Suzuki H, Sawada M, Serra M, Biggio G, Latrofa A, Trapani G, Liso G. Bioconjugate Chem. 2007; 18:1397. Trapani G, Laquintana V, Denora N, Trapani A, Lopedota A, Latrofa A, Franco M, Serra M, Pisu MG, Floris I, Sanna E, Biggio G, Liso G. J. Med. Chem. 2005; 48:292. [PubMed: 15634024]

[iv]. For multicomponent approach limited to synthesis of 3-aminoimidazo[1,2-*a*]pyridine derivatives, see: Rousseau AL, Matlaba P, Parkinson CJ. Tetrahedron Lett. 2007; 48:4079. DiMauro EF, Kennedy JM. J. Org. Chem. 2007; 72:1013. [PubMed: 17253825] Lyon MA, Kercher TS. Org. Lett. 2004; 6:4989. [PubMed: 15606117] Masquelin T, Bui H, Brickley B, Stephenson G, Schwerkosked J, Hulmea C. Tetrahedron Lett. 2006; 47:2989.

[v]. For examples on synthesis of fused heterocycles via Cu and Pd-catalyzed 5-*exo-dig* heteroannulation, see: Martín R, Rodríguez Rivero M, Buchwald SL. Angew. Chem. Int. Ed. 2006; 45:7079. Bakherad M, Nasr-Isfahani H, Keivanloo A, Sang G. Tetrahedron Lett. 2008; 49:6188. Bakherad M, Nasr-Isfahani H, Keivanloo A, Doostmohammadi N. Tetrahedron Lett. 2008; 49:3819.

[vi]. For selected examples of Cu-catalyzed syntheses of propargylamines via TCC approach, see: Patil MK, Keller M, Reddy BM, Pale P, Sommer J. Eur. J. Org. Chem. 2008:4440. Kantam ML, Laha S, Yadav J, Bhargava S. Tetrahedron Lett. 2008; 49:3083. For Au-catalyzed, see: Loa VK-Y, Kung KK-Y, Wong M-K, Che C-M. J. Organomet. Chem. 2009; 694:583. Zhang X, Corma A. Angew. Chem. 2008; 120:4430. Angew. Chem. Int. Ed. 2008; 47:4358. Kidwai M, Bansal V, Kumarb A, Mozumdar S. Green Chem. 2007; 9:742. For other transition metal-catalyzed, see: Zhang Y, Li P, Wang M, Wang L. J. Org. Chem. 2009; 74:4364. [PubMed: 19422248] Li P, Zhang Y, Wang L. Chem. Eur. J. 2009; 15:2045. [PubMed: 19177481] For enantioselective version, see: Li C-J, Wei C. Chem. Comm. 2002:268. [PubMed: 12120398] Gommermann N, Koradin C, Polborn K, Knochel P. Angew. Chem. Int. Ed. 2003; 42:5763. Knöpfel TF, Aschwanden P, Ichikawa T, Watanabe T, Carreira EM. Angew. Chem. 2004; 116:6097. Angew. Chem. Int. Ed. 2004; 43:5971. Bisai A, Singh VK. Org. Lett. 2006; 8:2405. [PubMed: 16706537]

[vii]. Yan B, Liu Y. Org. Lett. 2007; 9:4323. [PubMed: 17854200]

[viii]. Apparently, CuCl is a better catalyst for the synthesis of propargylamine **4** via three component coupling reaction of corresponding 2-aminopyridine, aldehyde and acetylene, whereas $Cu(OTf)_2$ is more efficient for the subsequent 5-*exo-dig* cyclization of **4** toward imidazo[1,2-a]pyridyl core **5**. See ref. 9 and discussion therein.

[ix]. For employment of Cu(I)/Cu(II) binary system in the synthesis of benzofurans, see: Sakai N, Uchida N, Konakahara T. Tetrahedron Lett. 2008; 49:3437.

[x]. See Supporting Information for details.

[xi]. Sumalatha Y, Reddy TR, Reddy PP, Satyanarayana B. ARKIVOC. 2008; 2:315. Allen J, Parent G, Tizot A. J. Labelled Compd. Radiopharm. 1986; 23:807. Allen J, Tizot A. J. Labelled Compd. Radiopharm. 1986; 23:393. For patents, see Supporting Information.

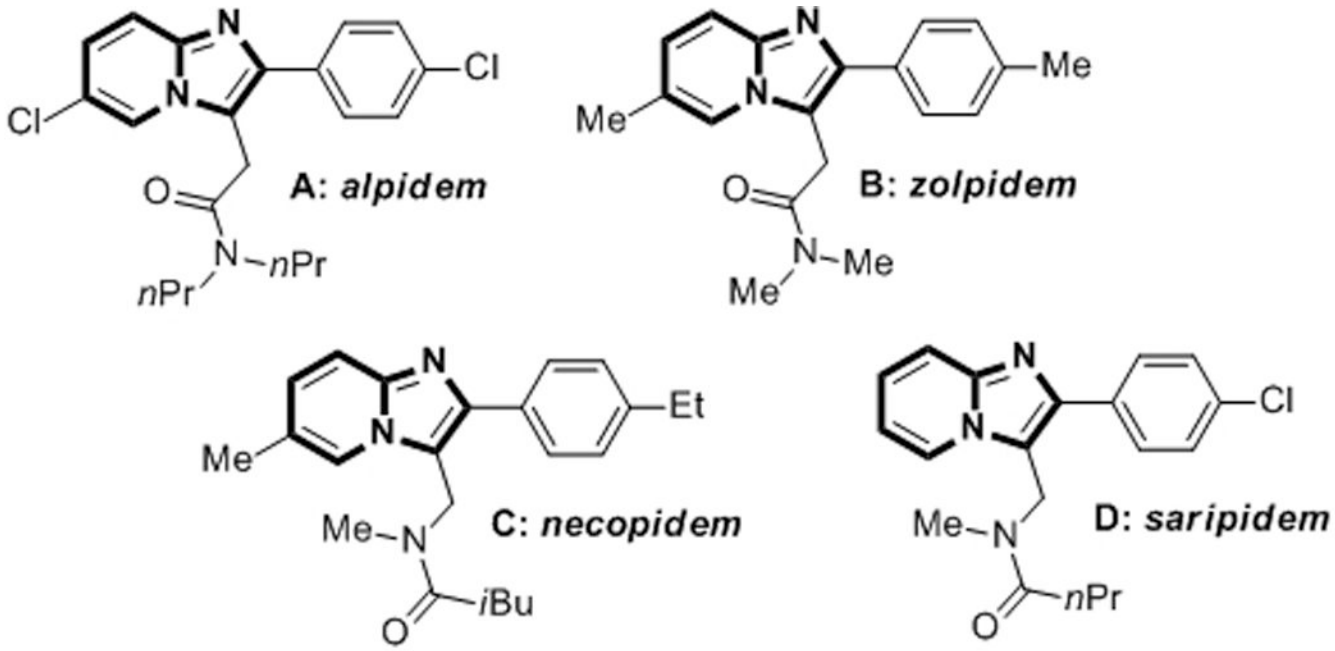

Figure 1.
Imidazo[1,2-*a*]pyridine-Based Drugs.

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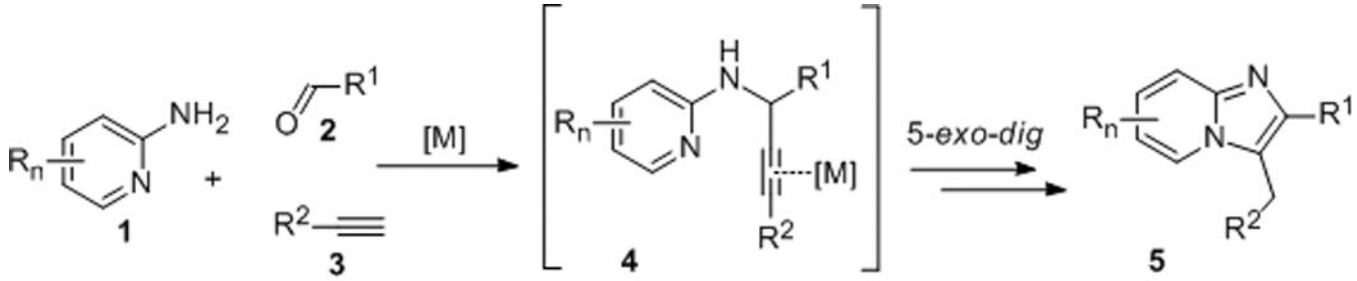

Scheme 1.
Synthesis of Imidazopyridines via TCC Approach.

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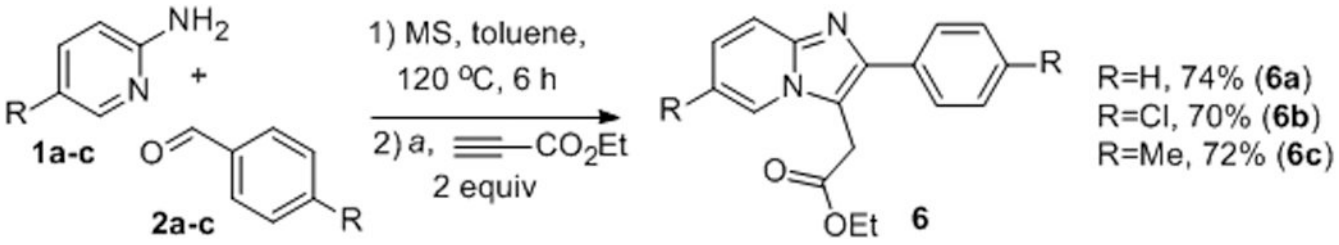

Scheme 2.

Model Studies of One-Pot TCC Reaction. *a*: CuCl (5 mol%), $Cu(OTf)_2$ (5 mol%), RT, 1 h. MS = 4Å molecular sieves.

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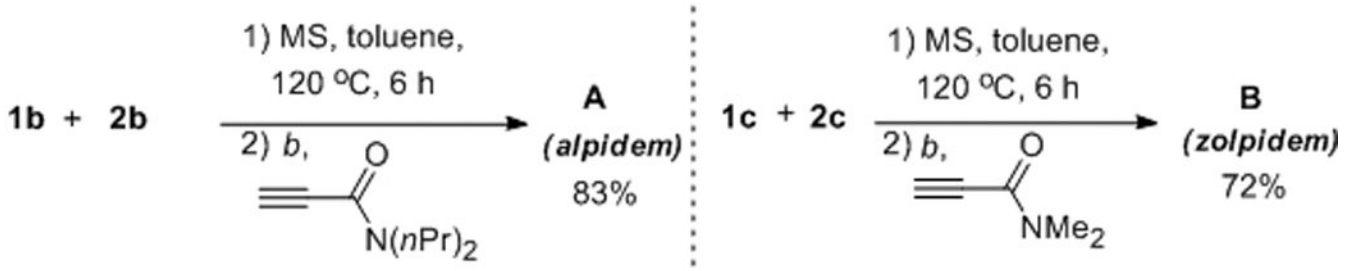

Scheme 3.

One-Pot Synthesis of Alpidem and Zolpidem. *b*: CuCl (5 mol%), $Cu(OTf)_2$ (5 mol%), 40°C, 4 h.

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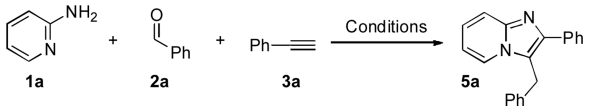
Table 1

Optimization of TCC Reaction Conditions.[a]



Entry	Catalyst [mol%]	Solvent	*T* [°C]	5a GC Yield [%][b]
1	$NaAuCl_4 \cdot 2H_2O$ [5]	toluene	120	0
2	$Cu(OTf)_2$ [5]	toluene	120	10
3	CuCl [10]	toluene	120	55
4	CuCl [50]	toluene	120	74
5	CuCl [5], $Cu(OTf)_2$ [5]	MeCN	100	15
6	CuCl [5], $Cu(OTf)_2$ [5]	DMA	120	78
7	**CuCl [5], $Cu(OTf)_2$ [5]**	**toluene**	**120**	**93**
8	CuCl [5], $Cu(OTf)_2$ [5]	toluene	120	76[c]

[a]Reaction conditions: 2-aminopyridine (0.1 mmol), benzaldehyde (0.105 mmol), acetylene (0.11 mmol), CuCl (0.005 mmol), $Cu(OTf)_2$ (0.005 mmol), solvent (1 M, 0.1 mL), 16 h.

[b]Yields were determined by GC-MS analysis versus internal standard.

[c]Reaction was performed under air.

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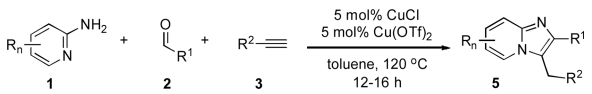
Table 2

Synthesis of Imidazoheterocycles.[10]



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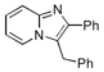
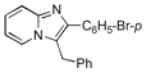
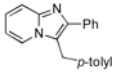
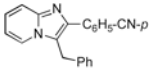
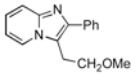
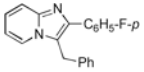
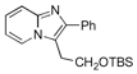
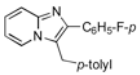
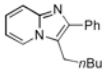
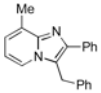
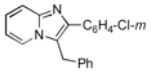
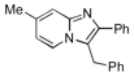
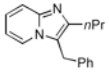
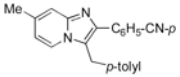
1	 **5a**	92	12	 **5l**	89
2	 **5b**	90	13	 **5m**	80
3	 **5c**	79	14	 **5n**	90
4	 **5d**	70	15	 **5o**	86
5	 **5e**	44[b]	16	 **5p**	50[c]
6	 **5f**	81	17	 **5q**	61
7	 **5g**	56[b]	18	 **5r**	87

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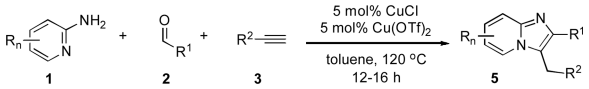
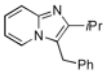
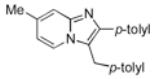
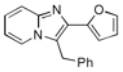
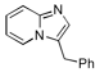
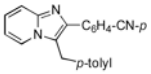
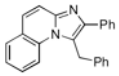
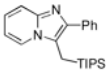
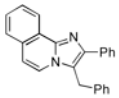


Entry	Product	Yield [%][a]	Entry	Product	Yield [%][a]
8	 **5h**	60	19	 **5s**	83
9	 **5i**	78	20	 **5t**	50[c]
10	 **5j**	82	21	 **5u**	70
11	 **5k**	73	22	 **5v**	65

[a]Yield of isolated product. TIPS = triisopropylsilyl.

[b]Product decomposes upon prolonged heating.

[c]Some amounts of 2-aminopyridine and benzaldehyde remained unreacted.

[d]Corresponding imine was isolated in 48% yield.