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Copper(II) triflate-catalyzed highly efficient synthesis of *N*-substituted 1,4-dihydropyridine derivatives via three-component cyclizations of alkynes, amines, and α,β-unsaturated aldehydes

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ABSTRACT

A copper(II) triflate-catalyzed three-component cyclization of alkynes, amines, and α,β-unsaturated aldehydes was developed to give various 1,4-dihydropyridines in good to high yields. In addition, this efficient and practical protocol proceeded smoothly in gram scale even when the catalytic loading was reduced to 1 mol %.

Introduction

Among numerous bioactive compounds in the pharmaceutical and medicinal chemistry, 1,4-dihydropyridines (1,4-DHPs) are one of the most common and privileged skeletons in many antihypertension drugs,[1] calcium-channel-modulating agents,[2] MDR-modulators,[3] HIV-1 protease inhibitors,[4] chemosensitizers in tumor therapy,[5] and compounds with many other activities.[6] Due to their high frequency in small molecular drugs, 1,4-DHPs have attracted more and more chemists in this area to synthesize various functional 1,4-dihydropyridines. Since the report of the Hantzsch reaction with an amine, an aldehyde, and two 1,3-dicarbonyl compounds, various strategies involving different substrates and catalysts have been developed for the synthesis of these useful compounds,[7] and most of them are based on the multicomponent reactions (MCRs).[8]

In 2008, Sambri and co-workers reported a multicomponent domino reaction for synthesis of substituted 1,4-dihydropyridines from aryl amines, β-dicarbonyl compounds, and ethyl propiolate that promoted by $Mg(ClO_4)_2$.[8k] Balalaie's group found that 1,4-dihydropyridine derivatives could be obtained from primary amine, methyl (arylmethylide) pyruvates, and dialkyl acetylenedicarboxylate in the presence of 40 mol % of $ZnCl_2$.[8t] Recently, Wan reported a three-component reaction of terminal alkynes, amines, and α,β-unsaturated aldehydes (Scheme 1c).[8y] In the presence of 30 mol % of piperazine and 80 mol % of *p*-tolsulfonic acid (p-TSA), 1,4-DHPs were obtained with 57–85% yields. It encourages us to develop a more efficient catalyst system to approach the synthesis of 1,4-dihydropyridines. Herein, we report a highly efficient and practical $Cu(OTf)_2$-catalyzed three-component reaction of alkynes, amines, and α,β-unsaturated aldehydes to afford 1,4-DHPs with good yields (Scheme 1d). In order to show the synthetic utility of this protocol, a large scale experiment (6 mmol) with only 1 mol % Cu $(OTf)_2$ catalyst was also performed to give the expected 1,4-DHPs in 94% yield (1.78 g).

Results and discussion

In a prototype experiment, the three-component reaction of α-methyl cinnamaldehyde **1a**, aniline **2a**, and ethyl propiolate **3a** were treated with **5** mol % Lewis acid in DCE at 70 °C. The reaction parameters optimized included temperature, solvent, and Lewis acid. As shown in Table 1, no product was formed in the absence of Lewis acids. A wide range of commercially available triflates including $Fe(OTf)_3$, $La(OTf)_3$, $In(OTf)_3$, $Yb(OTf)_3$, $Y(OTf)_3$, $Pr(OTf)_3$, and $Bi(OTf)_3$ were investigated, however only traces of the desired product were formed. Then a variety of copper salts such as 2CuOTf·toluene, CuCl, $Cu(MeCN)_4BF_4$, $Cu(OAc)_2$, $Cu(ClO_4)_2·6H_2O$,

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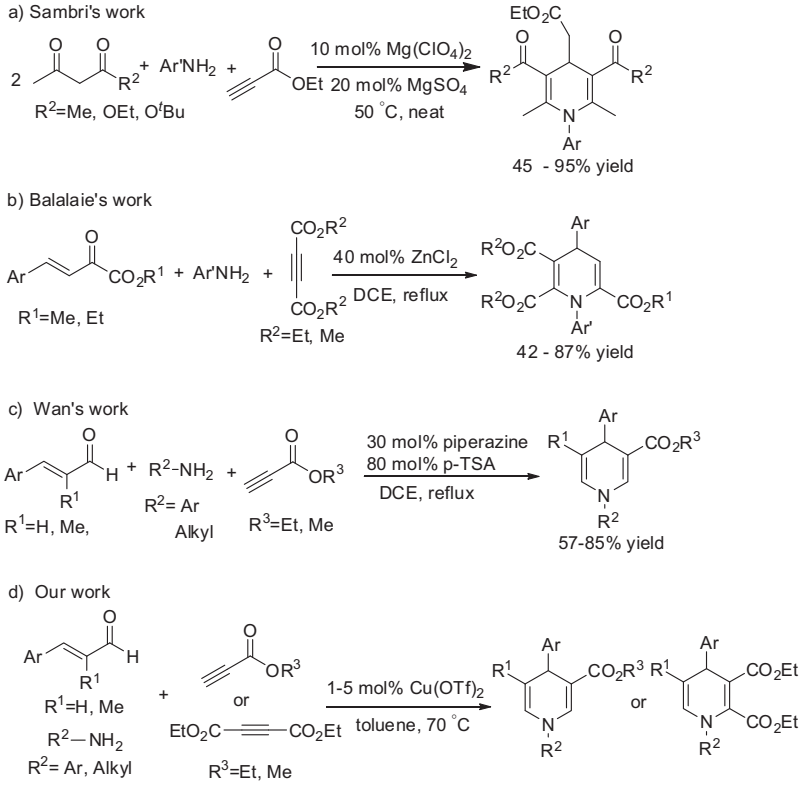
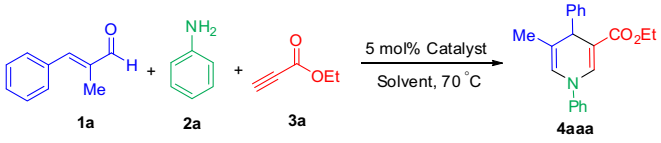


Scheme 1. Three-component reaction for synthesis of 1,4-DHPs.

Table 1
Optimization of the reaction conditions[a]



Entry	Triflate	Solvent	Time (h)	Yield (%)[b]
1[c]	None	DCE	72	NR
2[c]	2CuOTf·toluene	DCE	72	57
3[c]	CuCl	DCE	72	NR
4[c]	$Cu(MeCN)_4BF_4$	DCE	72	Trace
5[c]	$Cu(OAc)_2$	DCE	72	NR
6	$Cu(ClO_4)_2·6H_2O$	DCE	12	81
7	$Cu(OTf)_2$	DCE	2	87
8	$Cu(OTf)_2$	THF	6	86
9	$Cu(OTf)_2$	DMF	12	82
10	$Cu(OTf)_2$	Dioxane	24	79
11	$Cu(OTf)_2$	DME	12	72
12	$Cu(OTf)_2$	Toluene	2	92
13[d]	$Cu(OTf)_2$	Toluene	1	89
14[e]	$Cu(OTf)_2$	Toluene	12	80

[a] Reaction conditions: **1a** (0.3 mmol), **1a**/**2a**/**3a**/catalyst (1.0:1.2:2.0:0.05), all the reagents were intermediately added to 2 mL of solvent under Ar, then stirring at 70 °C for indicated period of time.
[b] Yield of isolated product after column chromatography.
[c] The reaction was not completed.
[d] The reaction was stirred at 90 °C.
[e] The reaction was stirred at 50 °C.

and $Cu(OTf)_2$ were also applied to this reaction (Table 1, entries 2–7). To our delight, the expected product **4aaa** was obtained with 87% yield when the reaction was catalyzed with $Cu(OTf)_2$. Further solvent screening revealed that the efficiency and the yield of the product in toluene were higher than those obtained in other solvents such as DCE, THF, DMF, Dioxane, and DME (Table 1, entries 7–12). In addition, lowering or raising the reaction temperature would not help to improve the yield (Table 1, entries 13 and 14). Optimal condition was obtained when α-methyl cinnamaldehyde **1a**, aniline **2a**, and ethyl propiolate **3a** in the ratio of 1:1.2:2 were

stirred in toluene with 5 mol % of $Cu(OTf)_2$ at 70 °C, resulting dihydropyridine **4aaa** in 92% isolated yield (Table 1, entry 12).

With the optimized conditions in hands, a range of aromatic and aliphatic amines was investigated. As shown in Table 2, the electronic factor of anilines showed no obvious influence on the yields of products and the rate of the reactions, but the reactions of more sterically hindered *ortho*-substituted anilines proceeded sluggishly to give the desired 1,4-DHPs in a lower yields (entries 6 and 16). Moreover, this catalytic system is still fit for aliphatic amines (Table 2, entries 18 and 19), though moderate yields were resulted. The configuration of the product was confirmed by X-ray crystal structure analysis (**3aja**, Fig. 1).[9]

To further broaden the substrate scope of this three-component cyclization, a variety of α- or β-substituted enals were explored under the optimal reaction conditions. We are happy to find that all the substituted enals reacted smoothly as well, and afforded the expected product with 71–92% yields (Table 3, entries 1–10). When ethyl propiolate **3b** was used instead of methyl propiolate **3a**, the yield of **4aab** was obtained in 87% (Table 3, entry 11).

Encouraged by these results, we turned our attention to study this three-component cyclization with internal alkyne acetylenedicarboxylate **5** (Scheme 2). Fortunately, the reaction proceeded smoothly in standard conditions, and gave the product **6** with 82% yield.

In order to show the synthetic utility of this protocol, we performed large scale experiments (20 fold example of Table 2, entries 1 and 11) with only 1 mol % $Cu(OTf)_2$ catalyst. Products **4aaa** and **4aka** were obtained with excellent yields (1.78 g, 94% and 1.87 g, 91% respectively) which were even better with the yields obtained in usual scale with 5 mol % catalyst loading. It is strongly demonstrated that this type of 1,4-dihydropyridines was easily prepared in large scale under this catalytic system (Scheme 3).

To study the mechanism, a series of control experiments are conducted and shown in Scheme 4. There are two possible routes

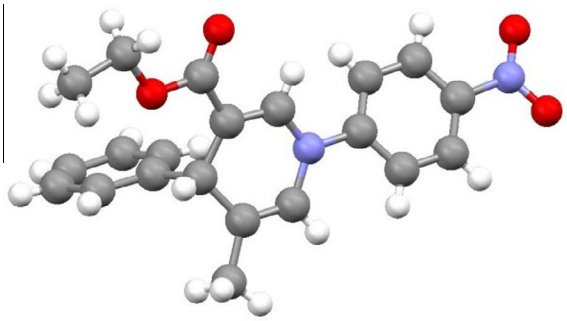
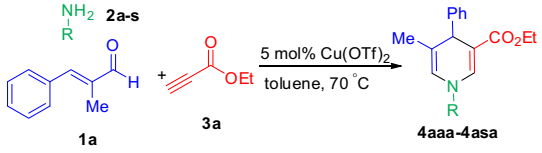


Figure 1. ORTEP drawing of **3aja**.

for this cyclization. One is [4+2] cyclization of imine **7** and alkyne **3a**, and another is [3+3] cyclization of enamine **8** and enal **1a**. In the presence of 5 mol % of $Cu(OTf)_2$, α-methyl cinnamaldehyde **1a** reacted with 4-methoxyl aniline **2k** smoothly and gave corresponding imine **7** equivalently. The imine **7** also can be formed from **1a** and **2k** even without any catalyst with longer time. Interestingly, no expected enamine **8** was detected (acetate functionalized 1,4-dihydropyridine **9** was obtained with 56% of yield[10]) by the reaction of 4-methoxyl aniline **2k** and ethyl propiolate **3a** with 5 mol % of $Cu(OTf)_2$, while enamine **8** could be obtained with 12% yield without any catalyst. Therefore, imine **7** is more stable and possible intermediate than enamine **8** under this reaction condition. Further experiments showed that both the pre-generated imine **7** and enamine **8** could be activated by $Cu(OTf)_2$ catalyst and react with ethyl propiolate **3a** and aldehyde **1a** respectively to give the desired 1,4-DHP **4aka**.

According to the control experiments, we proposed a plausible mechanism for this three-component cyclization with two

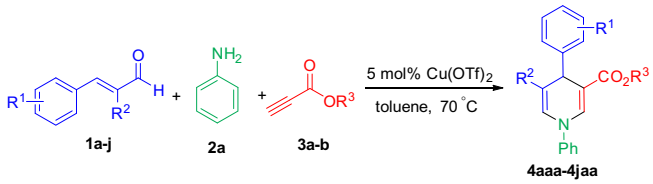
Table 2
Synthesis of *N*-substituted 1,4-dihydropyridines with various amines[a]



Entry	R	Time (h)	Product	Yield[b]
1	C_6H_5 **2a**	2	**4aaa**	92
2	4-FC_6H_4 **2b**	2	**4aba**	91
3	4-ClC_6H_4 **2c**	2	**4aca**	90
4	3-ClC_6H_4 **2d**	6	**4ada**	84
5	3,5-ClC_6H_3 **2e**	12	**4aea**	79
6[d]	2-ClC_6H_4 **2f**	72	**4afa**	61
7	4-BrC_6H_4 **2g**	6	**4aga**	86
8	4-IC_6H_4 **2h**	6	**4aha**	82
9	4-$CF_3C_6H_4$ **2i**	2	**4aia**	89
10	4-$NO_2C_6H_4$ **2j**	72	**4aja**	71
11	4-$OMeC_6H_4$ **2k**	2	**4aka**	88
12	4-$OCF_3C_6H_4$ **2l**	2	**4ala**	85
13	4-MeC_6H_4 **2m**	2	**4ama**	87
14	3-MeC_6H_4 **2n**	6	**4ana**	82
15	3,5-MeC_6H_3 **2o**	12	**4aoa**	78
16[d]	2-MeC_6H_4 **2p**	72	**4apa**	60
17	4-$^{i}PrC_6H_4$ **2q**	6	**4aqa**	85
18[d]	Bn **2r**	72	**4ara**	64
19[d]	Cy **2s**	72	**4asa**	68

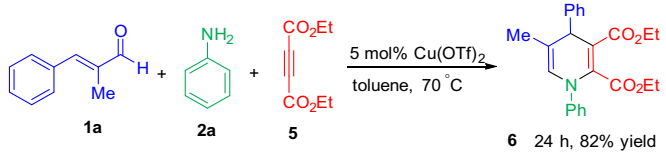
[a] Reaction conditions: **1a** (0.3 mmol), **1a**/**2**/**3a**/$Cu(OTf)_2$ (1.0:1.2:2.0:0.05), all the reagents were intermediately added to toluene (2 mL) under Ar, then stirring at 70 °C for indicated period of time.
[b] Yield of isolated product after column chromatography.
[d] The reaction was not completed.

Table 3
Synthesis of *N*-substituted 1,4-dihydropyridines with various aldehydes[a]

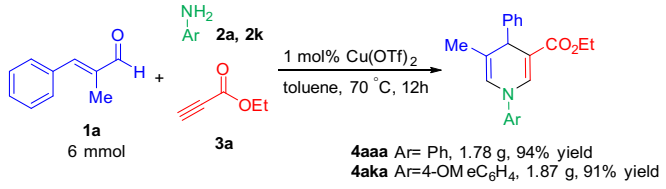


Entry	R_1	R_2	R_3	Time (h)	Product	Yield[b]
1	H	Me **1a**	Et **3a**	2	**4aaa**	92
2	H	H **1b**	Et **3a**	2	**4baa**	85
3	H	C_5H_{11} **1c**	Et **3a**	6	**4caa**	86
4	H	C_6H_{13} **1d**	Et **3a**	6	**4daa**	84
5	4-Me	H **1e**	Et **3a**	6	**4eaa**	75
6	4-OMe	H **1f**	Et **3a**	6	**4faa**	71
7	4-Br	H **1g**	Et **3a**	6	**4gaa**	78
8	4-Cl	H **1h**	Et **3a**	6	**4haa**	80
9	4-F	H **1i**	Et **3a**	6	**4iaa**	85
10	3-F	H **1j**	Et **3a**	6	**4jaa**	81
11	H	Me **1a**	Me **3b**	2	**4aab**	87

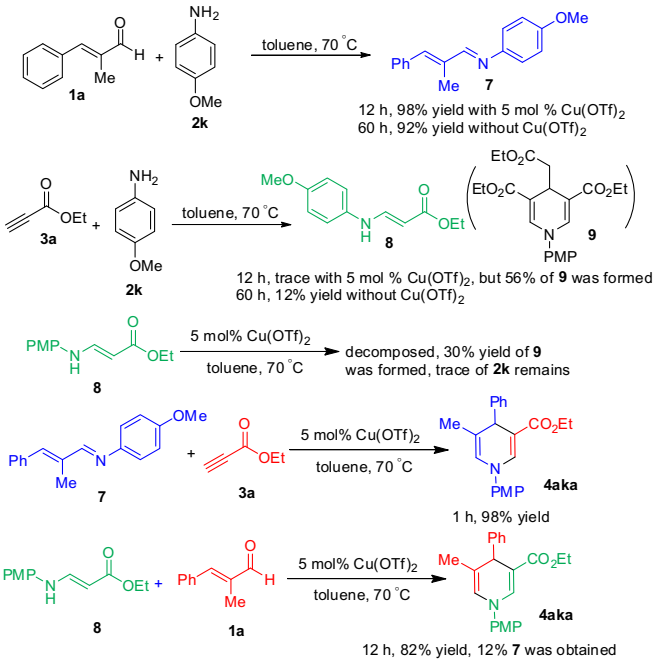
[a] Reaction conditions: **1** (0.3 mmol), **1**/**2a**/**3a**/$Cu(OTf)_2$ (1.0:1.2:2.0:0.05), all the reagents were intermediately added to toluene (2 mL) under Ar, then the mixture was stirred at 70 °C for indicated period of time.
[b] Yield of isolated product after column chromatography.



Scheme 2. Acetylenedicarboxylate involved three-component reaction for 1,4-DHPs.



Scheme 3. Gram scale reaction.

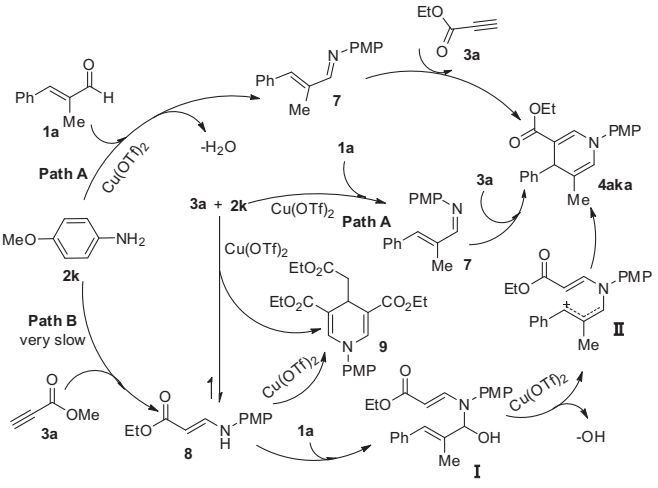


Scheme 4. Control experiments for mechanism study.

possible alternative reaction paths (Scheme 5). In the path **A**, imine **7** was formed via dehydration reaction of α-methyl cinnamaldehyde **1a** and 4-methoxyl aniline **2k** in the presence of catalyst before the desired product was obtained through aza-Diels–Alder reaction. The aza Diels–Alder reaction showed high regioselectivity that the most negatively charged nitrogen in diene connected with the most positively charged carbon in alkyne. As for path **B**, it looks more complicated and less possible than the former one. Enamine **8** was generated slowly through addition of **2k** and **3a**, and then intermediate **I** was produced via nucleophilic attack of NH to formyl group of **1a**. Consequently, the dehydration led to the formation of **4aka** via intermediate **II**; at the same time enamine **8** would partly undergo decomposition in the presence of $Cu(OTf)_2$ catalyst which then afforded imine **7** and 1,4-DHP same as path **A**.

Conclusions

In conclusion, we have successfully developed an efficient and practical three-component protocol for synthesis of 1,4-dihydropyridines in good to high yields. In addition, this reaction proceeded smoothly in gram scale when the catalytic loading was reduced to 1 mol %. Further investigations on asymmetric synthesis methodology of 1,4-dihydropyridines and their biological activities evaluation are ongoing in our laboratory.



Scheme 5. Proposed mechanisms for the three-component reaction.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.08.085.

References and notes

1. (a) Ghozlan, S. A. S.; Mohamed, M. F.; Ahmed, A. G.; Shouman, S. A.; Attia, Y. M.; Abdelhamid, I. A. *Arch. Pharm. Chem. Life Sci.* **2015**, *348*, 113–124; (b) Kumar, A.; Maurya, R. A.; Sharma, S.; Kumar, M.; Bhatia, G. *Eur. J. Med. Chem.* **2010**, *45*, 501–509.
2. (a) Gasco, A. M.; Ermondi, G.; Fruttero, R.; Gasco, A. *Eur. J. Med. Chem.* **1996**, *31*, 3–10; (b) Prasanthi, G.; Prasad, K. V. S. R. G.; Bharathi, K. *Eur. J. Med. Chem.* **2013**, *66*, 516–525.
3. (a) Baumert, C.; Günthel, M.; Krawczyk, S.; Hemmer, M.; Wersig, T.; Langner, A.; Molnár, J.; Lage, H.; Hilgeroth, A. *Bioorg. Med. Chem.* **2013**, *21*, 166–177; (b) Liu, Y.; Tan, H.; Yan, H.; Song, X. *Chem. Biol. Drug Des.* **2013**, *82*, 567–578; (c) von Nussbaum, F.; Li, V. M. J.; Allerheiligen, S.; Anlauf, S.; Bärfacker, L.; Bechem, M.; Delbeck, M.; Fitzgerald, M. F.; Gerisch, M.; Gielen-Haertwig, H.; Haning, H.; Karthaus, D.; Lang, D.; Lustig, K.; Meibom, D.; Mittendorf, J.; Rosentreter, U.; Schäfer, M.; Schäfer, S.; Schamberger, J.; Telan, L. A.; Tersteegen, A. *ChemMedChem* **2015**, *10*, 1163–1173; (d) Radadiya, A.; Khedkar, V.; Bavishi, A.; Vala, H.; Thakrar, S.; Bhavsar, D.; Shah, A.; Coutinho, E. *Eur. J. Med. Chem.* **2014**, *74*, 375–387.
4. Poondra, R. R.; Nallamelli, R. V.; Meda, C. L. T.; Srinivas, B. N. V.; Grover, A.; Muttabathula, J.; Voleti, S. R.; Sridhar, B.; Pal, M.; Parsa, K. V. L. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1104–1109.
5. Homraruen, D.; Sirijindalert, T.; Dubas, L.; Sukwattanasinitt, M.; Ajavakom, A. *Tetrahedron* **2013**, *69*, 1617–1621.
6. (a) Pal, S.; Singh, V.; Das, P.; Choudhury, L. H. *Bioorg. Chem.* **2013**, *48*, 8–15; (b) Mai, A.; Valente, S.; Meade, S.; Carafa, V.; Tardugno, M.; Nebbioso, A.; Galmozzi, A.; Mitro, N.; De Fabiani, E.; Altucci, L.; Kazantsev, A. *J. Med. Chem.* **2009**, *52*, 5496–5504.
7. (a) Ishar, M. P. S.; Kumar, K.; Kaur, S.; Kumar, S.; Girdhar, N. K.; Sachar, S.; Marwaha, A.; Kapoor, A. *Org. Lett.* **2001**, *3*, 2133–2136; (b) Barluenga, J.; de la Rúa, R. B.; de Sáa, D.; Ballesteros, A.; Tomás, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4981–4983; (c) Vohra, R. K.; Bruneau, C.; Renaud, J.-L. *Adv. Syn. Catal.* **2006**, *348*, 2571–2574; (d) Cui, S.-L.; Wang, J.; Lin, X.-F.; Wang, Y.-G. *J. Org. Chem.* **2007**, *72*, 7779–7782; (e) Kikuchi, S.; Iwai, M.; Murayama, H.; Fukuzawa, S.-I. *Tetrahedron Lett.* **2008**, *49*, 114–116; (f) Singh, L.; Ishar, M. P. S.; Elango, M.; Subramanian, V.; Gupta, V.; Kanwal, P. *J. Org. Chem.* **2008**, *73*, 2224–2233; (g) Yoshida, K.; Inokuma, T.; Takasu, K.; Takemoto, Y. *Molecules* **2010**, *15*, 8305–8326; (h) Auria-Luna, F.; Marqués-López, E.; Mohammadi, S.; Heiran, R.; Herrera, R. *Molecules* **2015**, *20*, 15807–15826.
8. (a) Kiruthika, S. E.; Vidhya Lakshmi, N.; Banu, B. R.; Perumal, P. T. *Tetrahedron Lett.* **2011**, *52*, 6508–6511; (b) Sun, J.; Sun, Y.; Gao, H.; Yan, C.-G. *Eur. J. Org. Chem.* **2011**, *2011*, 6952–6956; (c) Wan, J.-P.; Liu, Y. *RSC Adv.* **2012**, *2*, 9763; (d) Nair, V.; Jose, A.; Lakshmi, R. R.; Suresh, E. *Org. Biomol. Chem.* **2012**, *10*, 7747–7752; (e) Zhang, L.-J.; Wu, Q.; Sun, J.; Yan, C.-G. *Beilstein J. Org. Chem.* **2013**, *9*, 846–851; (f) Kiruthika, S. E.; Perumal, P. T. *RSC Adv.* **2014**, *4*, 3758–3767; (g) Chen, H.-S.; Guo, R.-Y. *Monatsh. Chem.* **2015**, *146*, 1355–1362; (h) Dhinakaran, I.; Padmini, V.; Bhuvanesh, N. *J. Chem. Sci.* **2015**, *127*, 2201–2209; (i) Safaei-Ghomi, J.; Heidari-Baghbahadorani, E.; Shahbazi-Alavi, H.; Asgari-Kheirabadi, M. *RSC Adv.* **2015**, *5*, 18145–18152; (j) Sridharan, V.; Perumal, P. T.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **2007**, *63*, 4407–4413; (k) Bartoli, G.; Bosco, M.; Galzerano, P.; Giri, R.; Mazzanti, A.; Melchiorre, P.; Sambri, L. *Eur. J. Org. Chem.* **2008**, *2008*, 3970–3975; (l) Das, B.; Suneel, K.; Venkateswarlu, K.; Ravikanth, B. *Chem. Pharm. Bull.* **2008**, *56*, 366–368; (m) Jiang, J.; Yu, J.; Sun, X.-X.; Rao, Q.-Q.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 2458–2462; (n) Kumar, A.; Maurya, R. A. *Tetrahedron* **2008**, *64*, 3477–3482; (o) Ramesh, D.; Rajaram, S.; Reddy, T. S.; Manasa, G.; Narasimhulu, M.; Mahesh, K. C.; Venkateswarlu, Y. *Chin. J. Chem.* **2011**, *29*, 2471–2475; (p) Singh, S. K.; Singh, K. N. *Monatsh. Chem.* **2011**, *143*, 805–808; (q) Sueki, S.; Takei, R.; Abe, J.; Shimizu, I. *Tetrahedron Lett.* **2011**, *52*, 4473–4477; (r) Sun, J.; Wu, Q.; Xia, E.-Y.; Yan, C.-G. *Eur. J. Org. Chem.* **2011**, *2011*, 2981–2986; (s) Yang, S.-H.; Zhao, F.-Y.; Lü, H.-Y.; Deng, J.; Zhang, Z.-H. *J. Heterocycl. Chem.* **2012**, *49*, 1126–1129; (t) Balalaie, S.; Baoosi, L.; Tahoori, F.; Rominger, F.; Bijanzadeh, H. R. *Tetrahedron* **2013**, *69*, 738–743; (u) Deng, Y.; Liu, L.; Sarkisian, R. G.; Wheeler, K.; Wang, H.; Xu, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 3663–3667; (v) Liu, L.; Sarkisian, R.; Deng, Y.; Wang, H. *J. Org. Chem.* **2013**, *78*, 5751–5755; (w) Reddy, T. R.; Reddy, G. R.; Reddy, L. S.; Meda, C. L. T.; Parsa, K. V. L.; Kumar, K. S.; Lingappa, Y.; Pal, M. *Eur. J. Med. Chem.* **2013**, *62*, 395–404; (x) Ma, Y.-L.; Wang, K.-M.; Lin, X.-R.; Yan, S.-J.; Lin, J. *Tetrahedron* **2014**, *70*, 6578–6584; (y) Wan, J.-P.; Lin, Y.; Jing, Y.; Xu, M.; Liu, Y. *Tetrahedron* **2014**, *70*, 7874–7880; (z) Wan, J.; Zhou, Y.; Liu, Y.; Fang, Z.; Wen, C. *Chin. J. Chem.* **2014**, *32*, 219–226; (aa) Sueki, S.; Takei, R.; Zaitsu, Y.; Abe, J.; Fukuda, A.; Seto, K.; Furukawa, Y.; Shimizu, I. *Eur. J. Org. Chem.* **2014**, *2014*, 5281–5301; (ab) An, D.; Zhu, Z.; Zhang, G.; Gao, Y.; Gao, J.; Han, X.; Zheng, L.; Zhang, S. *Tetrahedron: Asymmetry* **2015**, *26*, 897–906; (ac) Cao, S.; Zhong, S.; Hu, C.; Wan, J.-P.; Wen, C. *Chin. J. Chem.* **2015**, *33*, 568–572.
9. CCDC 1479211 [for **3aja**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
10. Hu, D.; Liu, Y.; Wan, J.-P. *Tetrahedron* **2015**, *71*, 6094–6098.