Iodoarene-catalyzed cyclizations of *N*-propargylamides and β-amidoketones: synthesis of 2-oxazolines

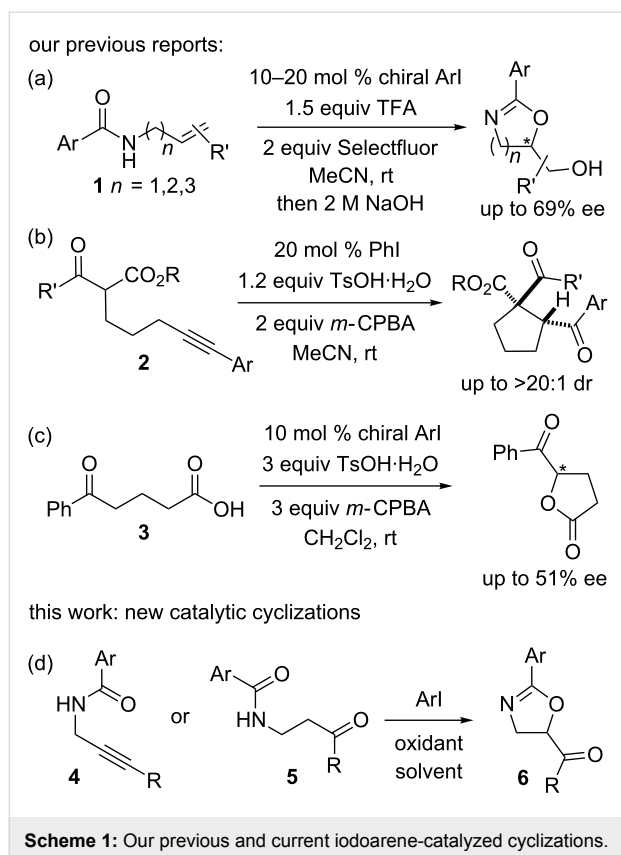Somaia Kamouka and Wesley J. Moran[*]

Abstract

Two complementary iodoarene-catalyzed methods for the preparation of 2-oxazolines are presented. The first involves the cyclization of *N*-propargylamides and the second involves the cyclization of β-amidoketones. These are proposed to proceed through different mechanisms and have different substrate scopes.

Introduction

Hypervalent iodine reagents are of increasing importance in organic synthesis owing to their ease-of-use, low toxicity and relative low cost. Importantly, a wide range of useful reactivity has been uncovered with these compounds and many reviews are available [1-5]. One major advance in recent years is the emergence of conditions to effect catalytic processes with substoichiometric quantities of iodine compound in the presence of an oxidant [6-11].

In this regard, we have reported the use of iodoarenes as precatalysts in the cyclizations of *N*-alkenylamides **1** [12], δ-alkynyl β-ketoesters **2** [13] and 5-oxo-5-phenylpentanoic acid (**3**, Scheme 1a–c) [14]. These three cyclizations exemplify three different proposed reaction pathways, i.e., iodine(III) activation of alkenes, alkynes and ketones. These cyclizations can be rendered enantioselective by the generation of non-racemic chiral iodine(III) species from chiral iodoarenes [15-17].
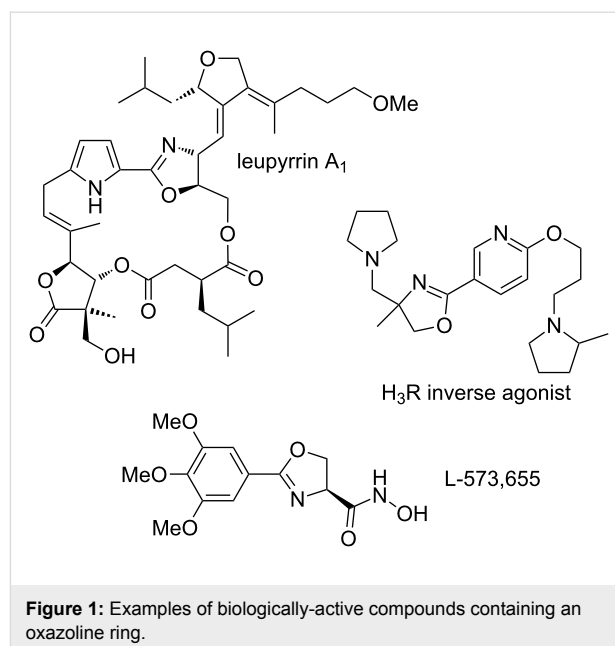
We wished to develop this cyclization methodology further and investigate the cyclization of the amide functional group on to alkynes and methylene groups adjacent to ketones in analogy to our previous work (Scheme 1d). This would provide two complementary routes to substituted 2-oxazolines, which are valuable heterocycles found in ligand scaffolds, natural products such as the leupyrrins [18,19], and potential pharmaceuticals (Figure 1) [20-22]. Traditional routes to this heterocycle include the dehydration of amino alcohols with carboxylic acids, however, this process typically requires forcing conditions such as heating at over 200 °C [23]. Several related processes that operate under milder conditions have been reported in recent years but they suffer from issues such as limited substrate scope or the requirement for expensive reagents or transition metal salts [24-29]. Saito and co-workers have reported the cyclization of propargylamides to form oxazoles rather than oxazolines under stoichiometric and, more recently, catalytic

Scheme 1: Our previous and current iodoarene-catalyzed cyclizations.

**Figure 1:** Examples of biologically-active compounds containing an oxazoline ring.

cantly lower yields of **6a** (Table 1, entries 5 and 6). Reducing the number of equivalents of oxidant and/or acid also led to lower yields (Table 1, entries 7–9). Importantly, formation of the six-membered ring was not observed under any conditions studied.

hypervalent iodine conditions [30,31]. Various other methods for the cyclization of unsaturated amides have been reported [32-36]. Gao and co-workers described the I_2-catalyzed cyclization of β-acylaminoketones using *tert*-butyl hydroperoxide as the oxidant; notably, adding DBU led to oxazole formation whereas adding K_2CO_3 generated oxazolines [37,38]. Our proposed new approaches to oxazoline formation utilise readily available starting materials and operate under mild organocatalytic conditions.

Results and Discussion

We initiated our study with readily available alkyne **4a** and subjected it to reaction conditions similar to those we have previously reported (Table 1). By using 2-iodoanisole as precatalyst in the presence of *p*-toluenesulfonic acid and *m*-chloroperbenzoic acid in acetonitrile, **4a** cyclized to **6a** in 92% yield as determined by ^{1}H NMR analysis of the crude reaction mixture (Table 1, entry 1). In line with our previous findings with *N*-alkenylamides, the use of iodobenzene in place of 2-iodoanisole provided a diminished yield of **6a** (Table 1, entry 2) [12]. The iodoarene was found to be essential for the conversion of the starting material, as its absence led to complete return of **4a** (Table 1, entry 3). Using Oxone as oxidant led to essentially no conversion of **4a** (Table 1, entry 4). Changing the acid to TFA or changing the solvent to CH_2Cl_2 led to signifi-

Table 1: Investigation of reaction conditions.

Entry	Deviations from the standard conditions	Yield [%]a
1	none	92 (73)b
2	iodobenzene instead of 2-iodoanisole	60
3	no 2-iodoanisole	0
4	Oxone instead of *m*-CPBA	<5
5	TFA instead of TsOH·H$_2$O	19
6	CH$_2$Cl$_2$ instead of MeCN	37
7	2 equiv *m*-CPBA and 2 equiv TsOH·H$_2$O	54
8	1 equiv *m*-CPBA and 1 equiv TsOH·H$_2$O	44
9	3 equiv *m*-CPBA and 1 equiv TsOH·H$_2$O	41

aDetermined by NMR analysis by comparison to a known quantity of 1,3,5-trimethoxybenzene. bYield of isolated compound.

With the optimal cyclization conditions in hand, the scope of this cyclization process was investigated for a range of propargylamides **4** which are readily accessible from propargylamine by amidation and Sonogashira coupling (Scheme 2) [39]. The cyclization was successful in all cases studied with various arylamide and alkyne substituents. All functional groups were well tolerated apart from an alkyne terminated with an alkyl substituted arene which led to a diminished yield of product, i.e., **6g**.

Scheme 2: 2-Iodoanisole-catalyzed cyclization of *N*-propargylamides.
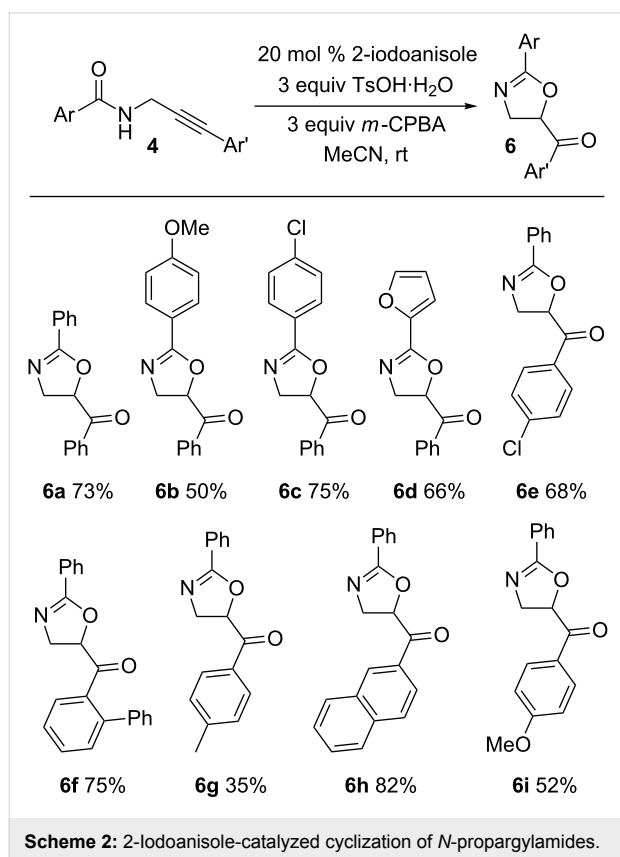
The mechanism of this cyclization is proposed to proceed though activation of the alkyne by an in situ generated iodine(III) species followed by intramolecular attack by the amide (Scheme 3). Subsequent addition of water leads to the loss of the iodoarene and tautomerization of the resulting enol generates the ketone **6**.

With these results in hand, we envisaged an alternative approach to 2-oxazoline formation through the iodoarene-catalyzed cyclization of β-amidoketones **5**. These are readily prepared by alkylation of the corresponding β-ketoester followed by decarboxylation (Scheme 4) [40,41].
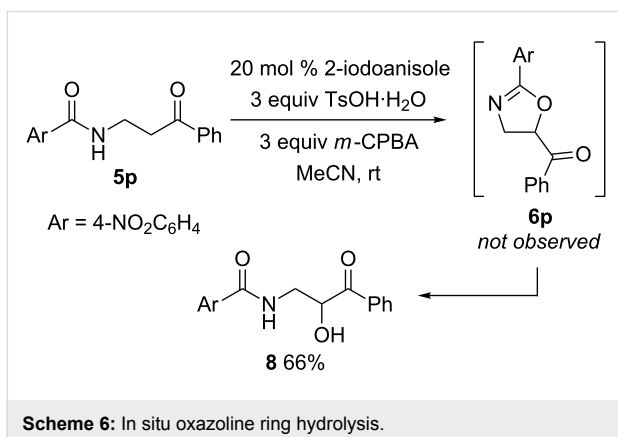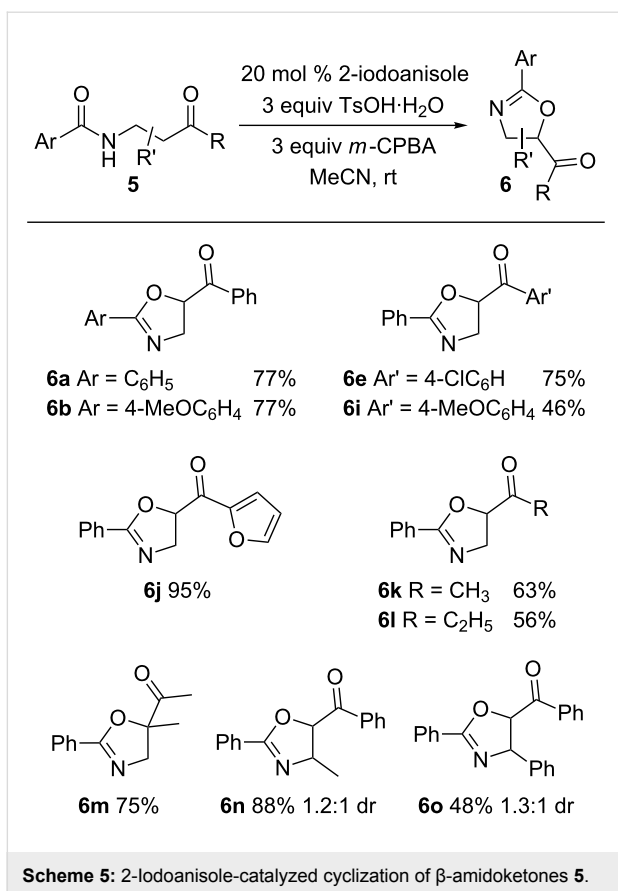
The cyclization of β-amidoketones **5** was successful with the same conditions as propargylamides **4** (Scheme 5). In line with

Scheme 3: Postulated mechanism for *N*-propargylamide cyclization.

Scheme 4: Synthesis of β-amidoketones **5**.
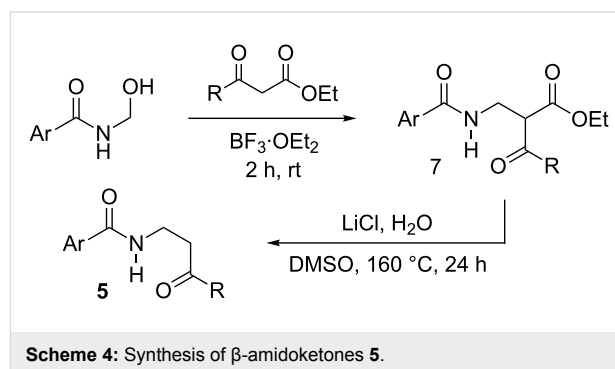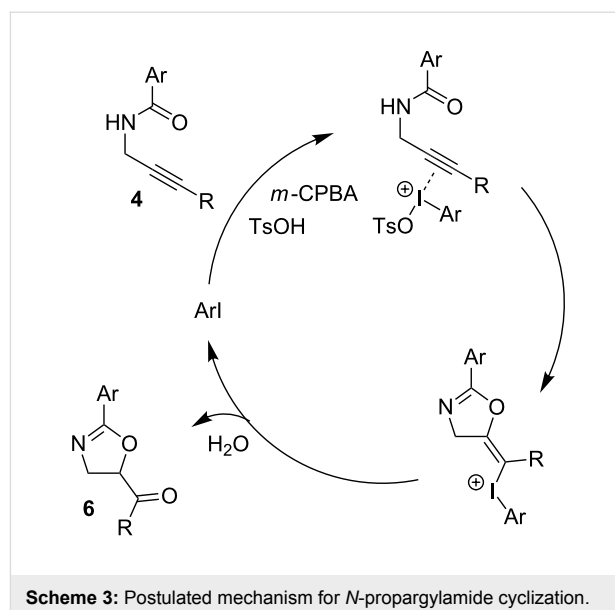
the results for the propargylamides, iodobenzene was an inferior pre-catalyst to 2-iodoanisole and other oxidants, acids and solvents led to lower yields of **6**.

The scope of this cyclization process was explored and different aromatic amide and ketone groups were well tolerated. Alkylketone substrates were also successfully converted to 2-oxazolines. Installation of substituents on the tether led to facile formation of product **6m** containing a quaternary carbon and compounds **6n** and **6o** but without any observed diastereoselectivity. Interestingly, the selectivity for **6o** could be improved to 5:1 by substituting *p*-toluenesulfonic acid with trifluoroacetic acid albeit with a loss of yield.

When the *p*-nitrophenylamide **5p** was subjected to the reaction conditions, the expected oxazoline **6p** was not observed (Scheme 6). Instead, alcohol **8** was isolated in 66% yield. Presumably, **6p** is formed under the reaction conditions but the oxazoline ring is readily hydrolysed due to the influence of the electron-withdrawing nitro group on the aromatic ring.

Scheme 5: 2-Iodoanisole-catalyzed cyclization of β-amidoketones **5**.

Scheme 6: In situ oxazoline ring hydrolysis.

The mechanism of this cyclization is proposed to proceed through the formation of iodine(III)-enolate **9** followed by intramolecular attack by the amide and release of the iodoarene (Scheme 7).

These two cyclizations are complementary, however, the reaction with β-amidoketones exhibits a superior substrate scope. In addition, the use of a chiral iodoarene should lead to enantioselective cyclizations of β-amidoketones; this is not possible with the propargylamides.

Scheme 7: Postulated mechanism for cyclization of β-amidoketones.
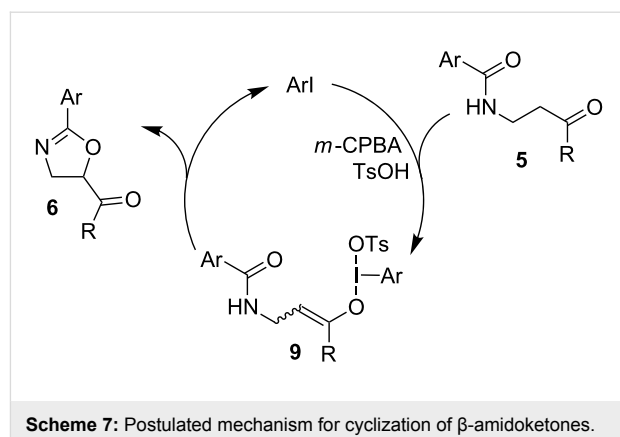
Conclusion

Two simple and convenient iodoarene-catalyzed methods to prepare substituted 2-oxazolines are reported. One involves the cyclization of propargylamides and the second of β-amidoketones. These two complementary procedures are efficient and showcase the utility of hypervalent iodine in catalytic procedures. Studies concerning the elucidation of reaction mechanisms are ongoing and will be reported in due course.

Experimental

General procedure for 2-iodoanisole-catalyzed cyclization of *N*-propargylamide 4 or β-amidoketone 5: Propargylamide **4** (1 equiv) or β-amidoketone **5** (1 equiv) was dissolved in acetonitrile (0.14 M) and 2-iodoanisole (0.2 equiv) was added, followed by *m*-CBPA (3 equiv) and *p*-TsOH·H$_2$O (3 equiv). The mixture was stirred overnight at room temperature, then saturated aqueous Na$_2$S$_2$O$_3$ solution and saturated aqueous NaHCO$_3$ solution were added and the mixture extracted with CH$_2$Cl$_2$. The organic layers were combined and dried with MgSO$_4$, filtered and concentrated under vacuum. The product was purified by flash chromatography (9:1 petroleum ether/ EtOAc) to provide oxazoline **6**. See Supporting Information File 1 for full experimental details.

Supporting Information

Supporting Information File 1

Full experimental details, characterization data and copies of NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/ supplementary/1860-5397-13-177-S1.pdf]

Acknowledgements

References

1. Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016,** *116,* 3328. doi:10.1021/acs.chemrev.5b00547
2. Zheng, Z.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Sci. China: Chem.* **2014,** *57,* 189. doi:10.1007/s11426-013-5043-1
3. Zhdankin, V. V. *Hypervalent Iodine Chemistry;* Wiley: Chichester, 2014.
4. Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008,** *108,* 5299. doi:10.1021/cr800332c
5. Brown, M.; Farid, U.; Wirth, T. *Synlett* **2013,** *24,* 424. doi:10.1055/s-0032-1318103
6. Yusubov, M. S.; Zhdankin, V. V. *Resour.-Effic. Technol.* **2015,** *1,* 49. doi:10.1016/j.reffit.2015.06.001
7. Dohi, T.; Kita, Y. *Chem. Commun.* **2009,** 2073. doi:10.1039/b821747e
8. Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006,** *45,* 4402. doi:10.1002/anie.200601817
9. Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005,** *127,* 12244. doi:10.1021/ja0542800
10. Singh, F. V.; Wirth, T. *Chem. – Asian J.* **2014,** *9,* 950. doi:10.1002/asia.201301582
11. Romero, R. M.; Wöste, T. H.; Muñiz, K. *Chem. – Asian J.* **2014,** *9,* 972. doi:10.1002/asia.201301637
12. Alhalib, A.; Kamouka, S.; Moran, W. J. *Org. Lett.* **2015,** *17,* 1453. doi:10.1021/acs.orglett.5b00333
13. Rodríguez, A.; Moran, W. J. *Org. Lett.* **2011,** *13,* 2220. doi:10.1021/ol200471w
14. Rodríguez, A.; Moran, W. J. *Synthesis* **2012,** *44,* 1178. doi:10.1055/s-0031-1290590
15. Berthiol, F. *Synthesis* **2015,** *47,* 587. doi:10.1055/s-0034-1379892
16. Parra, A.; Reboredo, S. *Chem. – Eur. J.* **2013,** *19,* 17244. doi:10.1002/chem.201302220
17. Liang, H.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2011,** *50,* 11849. doi:10.1002/anie.201106127
18. Herkommer, D.; Thiede, S.; Wosniok, P. R.; Dreisigacker, S.; Tian, M.; Debnar, T.; Irschik, H.; Menche, D. *J. Am. Chem. Soc.* **2015,** *137,* 4086. doi:10.1021/jacs.5b01894
19. Bode, H. B.; Irschik, H.; Wenzel, S. C.; Reichenbach, H.; Müller, R.; Höfle, G. *J. Nat. Prod.* **2003,** *66,* 1203. doi:10.1021/np030109v
20. Célanire, S.; Wijtmans, M.; Christophe, B.; Collart, P.; de Esch, I.; Dassesse, D.; Delaunoy, C.; Denonne, F.; Durieu, V.; Gelens, E.; Gillard, M.; Lallemand, B.; Lamberty, Y.; Lebon, F.; Nicolas, J.-M.; Quéré, L.; Snip, E.; Vanbellinghen, A.; Van houtvin, N.; Verbois, V.; Timmerman, H.; Talaga, P.; Leurs, R.; Provins, L. *ChemMedChem* **2009,** *4,* 1063. doi:10.1002/cmdc.200900055
21. Celanire, S.; Talaga, P.; Leurs, R.; Denonne, F.; Timmerman, H.; Lebon, F. Compounds comprising an oxazoline or thiazoline moiety, processes for making them, and their uses. WO Patent WO2006103057 A1, Oct 5, 2006.
22. Onishi, H. R.; Pelak, B. A.; Gerckens, L. S.; Silver, L. L.; Kahan, F. M.; Chen, M.-H.; Patchett, A. A.; Galloway, S. M.; Hyland, S. A.; Anderson, M. S.; Raetz, C. R. H. *Science* **1996,** *274,* 980. doi:10.1126/science.274.5289.980
23. Ilkgul, B.; Gunes, D.; Sirkecioglu, O.; Bicak, N. *Tetrahedron Lett.* **2010,** *51,* 5313. doi:10.1016/j.tetlet.2010.07.167
24. Brandstätter, M.; Roth, F.; Luedtke, N. W. *J. Org. Chem.* **2015,** *80,* 40. doi:10.1021/jo5016695
25. Garg, P.; Chaudhary, S.; Milton, M. D. *J. Org. Chem.* **2014,** *79,* 8668. doi:10.1021/jo501430p
26. Goud, D. R.; Pathak, U. *Synthesis* **2012,** *44,* 3678. doi:10.1055/s-0032-1317341
27. Takahashi, S.; Togo, H. *Synthesis* **2009,** 2329. doi:10.1055/s-0029-1216843
28. Sayama, S. *Synlett* **2006,** 1479. doi:10.1055/s-2006-941597
29. Schwekendiek, K.; Glorius, F. *Synthesis* **2006,** 2996. doi:10.1055/s-2006-950198
30. Asari, N.; Takemoto, Y.; Shinomoto, Y.; Yagyu, T.; Yoshimura, A.; Zhdankin, V. V.; Saito, A. *Asian J. Org. Chem.* **2016,** *5,* 1314. doi:10.1002/ajoc.201600383
31. Saito, A.; Matsumoto, A.; Hanzawa, Y. *Tetrahedron Lett.* **2010,** *51,* 2247. doi:10.1016/j.tetlet.2010.02.096
32. Senadi, G. C.; Guo, B.-C.; Hu, W.-P.; Wang, J.-J. *Chem. Commun.* **2016,** *52,* 11410. doi:10.1039/C6CC05138C
33. Liu, G.-Q.; Yang, C.-H.; Li, Y.-M. *J. Org. Chem.* **2015,** *80,* 11339. doi:10.1021/acs.joc.5b01832
34. Wang, N.; Chen, B.; Ma, S. *Adv. Synth. Catal.* **2014,** *356,* 485. doi:10.1002/adsc.201300959
35. Senadi, G. C.; Hu, W.-P.; Hsiao, J.-S.; Vandavasi, J. K.; Chen, C.-Y.; Wang, J.-J. *Org. Lett.* **2012,** *14,* 4478. doi:10.1021/ol301980g
36. Hashmi, A. S. K.; Blanco Jaimes, M. C.; Schuster, A. M.; Rominger, F. *J. Org. Chem.* **2012,** *77,* 6394. doi:10.1021/jo301288w
37. Minakata, S.; Morino, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2006,** *8,* 3335. doi:10.1021/ol061182q
38. Gao, W.-C.; Hu, F.; Huo, Y.-M.; Chang, H.-H.; Li, X.; Wei, W.-L. *Org. Lett.* **2015,** *17,* 3914. doi:10.1021/acs.orglett.5b01933
39. Bukšnaitienė, R.; Čikotienė, I. *Synlett* **2015,** *26,* 479. doi:10.1055/s-0034-1379320
40. Chao, M.; Hao, A.; Wang, H. *Org. Process Res. Dev.* **2009,** *13,* 645. doi:10.1021/op800313t
41. Kaku, H.; Imai, T.; Kondo, R.; Mamba, S.; Watanabe, Y.; Inai, M.; Nishii, T.; Horikawa, M.; Tsunoda, T. *Eur. J. Org. Chem.* **2013,** 8208. doi:10.1002/ejoc.201300936

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