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I_2/TBPB Mediated Oxidative Reaction of *N*-Tosylhydrazones with Anilines: Practical Construction of 1,4-Disubstituted 1,2,3-Triazoles under Metal-Free and Azide-Free Conditions

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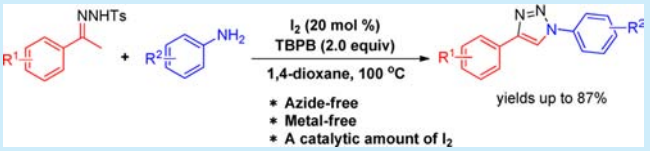
Supporting Information

ABSTRACT: An efficient I_2 (20 mol %)/TBPB mediated oxidative formal [4 + 1] cycloaddition of *N*-tosylhydrazones with anilines via C−N/N−N bond formation and S−N cleavage has been developed. This protocol represents a simple, general, and efficient approach for the construction of 1,2,3-triazoles under metal-free and azide-free conditions by utilizing a catalytic amount of I_2.



1,2,3-Triazoles are important *N*-heterocycles with wide applications in chemistry and material science. They serve as versatile synthetic intermediates, biological intermediates, lead molecules, linkers, and various drugs.[1] 1,2,3-Triazoles can be obtained conventionally through a Huisgen cycloaddition of azides and alkynes with poor regioselectivity.[2] The powerful and highly regioselective copper-catalyzed azide−alkyne-cycloaddition (CuAAC), developed independently by the Sharpless and Meldal groups,[4] affords 1,4-disubstituted 1,2,3-triazoles easily. With Sharpless's concept of "click chemistry",[5] 1,2,3-triazoles found numerous new applications[6] and their synthesis was popularized.[7−12] 1,2,3-Triazoles can also be prepared by RuAAC,[8] IrAAC,[9] as well as Pd-catalyzed reactions of alkenyl bromides with azides.[10] However, all of these reactions utilize heavy metals, which are not ideal for biological applications in view of their cytotoxicity. Recently, the organocatalytic reaction of ketones with azides has been investigated for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles and reported by Ramachary, Wang, and Bressy et al.[11] (Scheme 1, eq 1). More recently, Dehaen[12] developed a new organocatalytic strategy to synthesize 1,4,5-trisubstituted 1,2,3-triazoles with multicomponent reactions (MCRs) of readily available aldehydes, nitroalkanes, and organic azides (Scheme 1, eq 2). However, all of these reactions require sodium azides or organic azides, which are explosive. Therefore, the development of an efficient and straightforward synthesis of 1,2,3-triazoles from simple, readily accessible, and inexpensive materials is highly sought after.

To the best of our knowledge, the construction of 1,2,3-triazoles under metal-free and azide-free conditions has rarely been reported.[13] In 1986, Sakai et al. described the construction of 1,4-substituted triazole via the condensation of a primary amine and an α,α-dichlorotosylhydrazone under ambient reaction conditions (Scheme 1, eq 3).[13a] In 2012, Westermann et al. fully exploited the mechanism, scope, and limitations of the Sakai triazole formation reaction and illustrated the suitability of this transformation as a strategy for metal-free triazole construction (Scheme 1, eq 3).[13b] More recently, Zhang's group has reported the synthesis of 1,2,3-triazoles by the reaction of *N*-tosylhydrazones and anilines in the presence of 1.0 equiv of $Cu(OAc)_2$ and additive.[14] As part of our efforts on I_2/TBHP[15] or I_2/O_2-mediated reactions,[16] herein we demonstrate an efficient I_2 (20 mol %)/TBPB mediated oxidative formal [4 + 1] cycloaddition of *N*-tosylhydrazones with anlines with broad functional groups tolerance via C−N/N−N bond formation and S−N cleavage, which provides a simple and general approach for the construction of 1,2,3-triazoles in moderate to good yields under metal-free and azide-free conditions (Scheme 1, eq 4).

Scheme 1. Metal-Free Strategies for the Construction of 1,2,3-Triazoles

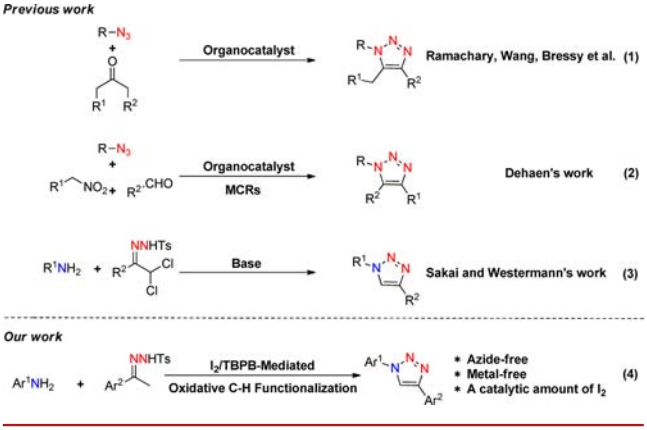


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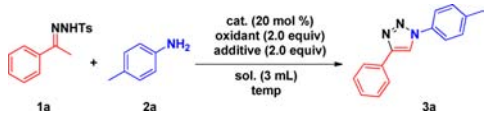
Table 1. Optimization of the Reaction Conditions[a]



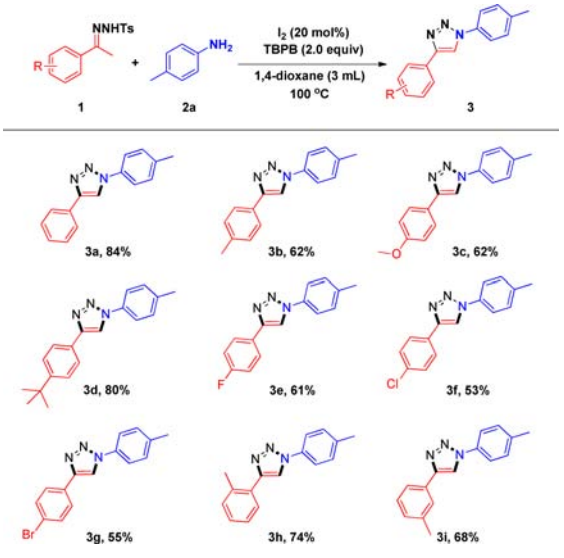
entry	catalyst (mol %)	temp (°C)	oxidant (equiv)	solvent (mL)	additive (equiv)	yield (LC–MS)
1	I_2 (20)	80	TBHP (2)	CH_3CN (3)		39
2	NaI (20)	80	TBHP (2)	CH_3CN (3)		13
3	KI (20)	80	TBHP (2)	CH_3CN (3)		10
4	NIS (20)	80	TBHP (2)	CH_3CN (3)		32
5	TBAI (20)	80	TBHP (2)	CH_3CN (3)		16
6	PIDA (20)	80	TBHP (2)	CH_3CN (3)		NR
7	I_2 (20)	80	TBPB (2)	CH_3CN (3)		67
8	I_2 (20)	80	TEMPO (2)	CH_3CN (3)		NR
9	I_2 (20)	80	CHP (2)	CH_3CN (3)		50
10	I_2 (20)	80	$K_2S_2O_8$ (2)	CH_3CN (3)		41
11	I_2 (20)	80	O_2 (2)	CH_3CN (3)		16
12	I_2 (20)	80	TBPB (2)	toluene (3)		68
13	I_2 (20)	80	TBPB (2)	DMF (3)		trace
14	I_2 (20)	80	TBPB (2)	DMSO (3)		26
15	I_2 (20)	80	TBPB (2)	1,4-dioxane (3)		75
16	I_2 (20)	80	TBPB (2)	DCE (3)		70
17	I_2 (20)	80	TBPB (2)	EtOH (3)		43
18	I_2 (20)	100	TBPB (2)	1,4-dioxane (3)		89 (84)[b]
19	I_2 (20)	100	TBPB (2)	1,4-dioxane (3)	HOAc (2)	86
20	I_2 (20)	100	TBPB (2)	1,4-dioxane (3)	PivOH (2)	86
21	I_2 (20)	100	TBPB (2)	1,4-dioxane (3)	Na_2CO_3 (2)	NR
22	I_2 (20)	100	TBPB (2)	1,4-dioxane (3)	Et_3N (2)	trace

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (0.1 mmol), oxidant (1.0 mmol), addtive (1.0 mmol), solvent (3 mL), 12 h; TBHP = *tert*-butyl hydroperoxide (70% in water); TBPB = *tert*-butyl peroxybenzoate; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy; CHP = cumene hydroperoxide. The yields were determined by LC analysis using biphenyl as the internal standard. [b]Isolated yield.

Our study was initiated by treating 4-methyl-*N*′-(1-phenylethylidene)benzenesulfonohydrazide **1a** and *p*-toluidine **2a** with I_2 (20 mol %) in the presence of TBHP (2.0 equiv) and CH_3CN (3 mL), 80 °C for 12 h. To our delight, 4-phenyl-1-(*p*-tolyl)-1*H*-1,2,3-triazole **3a** was formed in 39% yield by LC. In order to improve the yield of **3a**, we further screened different catalysts, solvents, oxidants, and reaction temperature, as well as additives (for more details see Supporting Information). As presented in Table 1, the reaction proceeded less efficiently in other iodine-containing catalysts such as NaI, KI, NIS, TBAI, and PIDA (Table 1, entries 2–6). After further screening of reaction was carried out in 1,4-dioxane, it was noted that the LC yield of **3a** could be increased to 75% (Table 1, entry 15). Moreover, a higher temperatrue could further increase the LC yield of **3a** to 89% in further (Table 1, entry 16). However, the yield did not improve significantly when HOAc or PivOH was added to the reaction (Table 1, entries 19 and 20). Furthermore, we failed to isolate the desired product **3a** when base (such as Na_2CO_3 and Et_3N) was added to the reaction. Thus, the optimized catalytic system was established: **1a** (0.5 mmol), **2a** (0.5 mmol), I_2 (0.1 mmol), TBPB (1.0 mmol), and 1,4-dioxane (3 mL) at 100 °C for 12 h.

With the optimized conditions in hand, we next investigated the substrate scope of this protocol (Scheme 2). A range of *N*-tosylhydrazones could be converted into the corresponding 1,4-disubstituted 1,2,3-triazoles in moderate-to-good yield (**3b–3i**, 53–80%). It was found that electron-donating groups (-CH_3, -OCH_3, -*t*-Bu) or halogen-substituted (-F, -Cl, -Br) substrates could react smoothly to afford the desired products. Notably, when *ortho*- or *meta*-CH_3 substituted *N*-tosylhydrazones were used as the substrates, a similar yield was observed (**3h**, 74%, **3i**, 68%). The structure of **3g** was further confirmed by X-ray crystallography.[17] It is interesting to note that some triazoles bearing halide functional group such as **3e–3g** show poor

Scheme 2. Reactions with Various *N*-Tosylhydrazones and 2a[a]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), I_2 (0.1 mmol), TBPB (1.0 mmol), 1,4-dioxane (3 mL), 100 °C, 12 h. Isolated yields.

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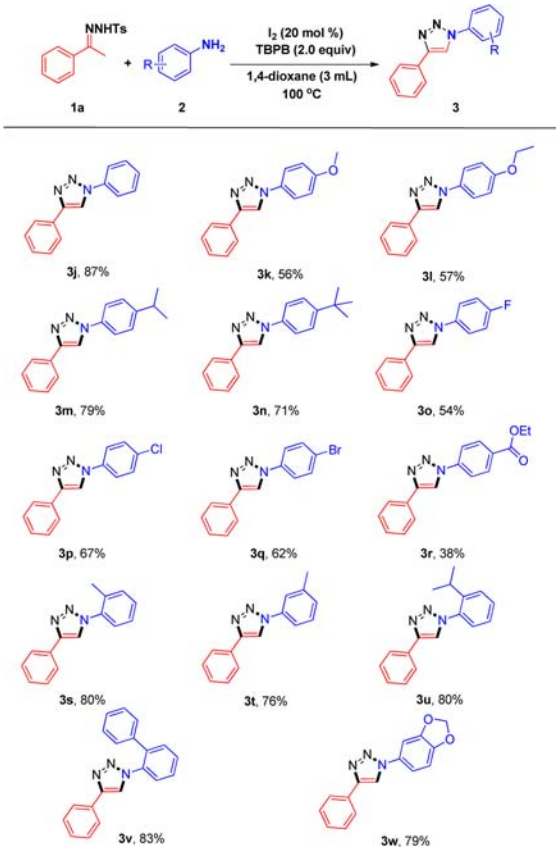
solubility in most of the deute rated solvents but have good solubility in deuterated trifluoroacetic acid.

Next, we explored the scope of aniline (Scheme 3). The reactions of aniline or 4-substituted anilines with *N*-tosylhydrazone took place smoothly to furnish the desired 1,4-disubstituted 1,2,3-triazoles **3j**–**3n** in 56–87% isolated yields. The fluoro, chloro, and bromo group could be tolerated in the reaction conditions to generate the desired functionalized 1,4-disubstituted 1,2,3-triazoles in moderate yields (**3o**–**3q**, 54–67%). The reaction of ethyl 4-aminobenzoate could also lead to the desired product **3r** in 38% yield, which is probably due to the electron-withdrawing effect of the ester group. Moreover, the reaction is not affected by the position of the substituents on the aromatic ring of anilines (**3s**–**3t**, 76–80%). When more sterically demanding substrates (2-isopropylaniline and [1,1′-biphenyl]-2-amine) were applied, the reaction proceeded smoothly to afford the desired products **3u** and **3v** in 80% and 83% yields, respectively. The structure of **3v** was also further confirmed by X-ray crystallography (for details see Supporting Information).[17]

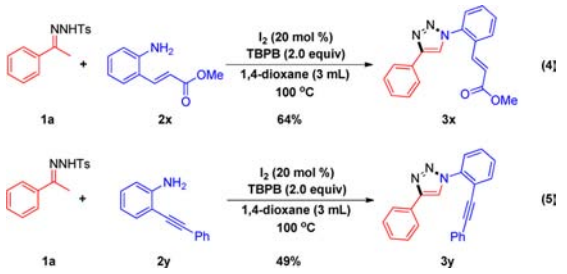
Scheme 3. Reactions of Various 1a and Anilines 2[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), I_2 (0.1 mmol), TBPB (1.0 mmol), 1,4-dioxane (3 mL), 100 °C, 12 h. Isolated yields.

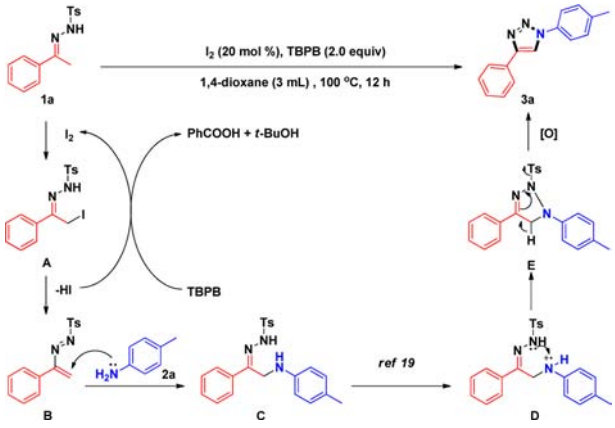
The synthetic expansion of this metal-free and azide-free oxidative formal [4 + 1] cycloaddition reaction are demonstrated in Scheme 4. When *N*-tosylhydrazone **1a** was treated with the alkenyl- or alkynyl-aniline (**3x**, **3y**), the desired products could be obtained in 64% and 49% yields, respectively. It should be noted that the optimized conditions could tolerate the alkene and alkyne functional groups.

Scheme 4. Synthetic Expansion of the Reaction of 1 and 2



Based on the results and the literature reports,[13,18,19] a plausible mechanism for the I_2/TBPB mediated oxidative formal [4 + 1] cycloaddition toward 1,2,3-triazoles is illustrated in Scheme 5. The *N*-tosylhydrazone **1a** is converted to a iodo-substituted intermediate **A**, in the presence of I_2. The azoalkene **B**[18] is formed by the leaving of HI along with a catalytic cycle of I^- being oxidized to I_2 by TBPB. Then, the addition of **2a** to the *in situ* generated azoalkene **B** to give **C**, which is further oxidized to give the corresponding radical cation **D**[19] under basic conditions. An intramolecular addition takes place to furnish the intermediate **E**. After a further oxidation of **E**, followed by a subsequent oxidation of **E** to give the desired product **3a**.

Scheme 5. A Plausible Mechanism



In conclusion, we have developed an efficient I_2/TBPB mediated oxidative formal [4 + 1] cycloaddition of *N*-tosylhydrazones with anilines. This transformation provides a practical synthetic method for the construction of 1,2,3-triazoles in the absence of azides and heavy metals. This protocol involves the functionalization of the C(sp^3)–H bond, the formation of C–N/N–N bonds, and the cleavage of S–N in one manipulation. Further studies to understand the mechanism of the I_2/TBPB mediated reaction and extend this protocol to synthetic applications are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*;Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. *5*, pp 669. (b) Abu-Orabi, S. T.; Atfah, M. A.; Jibril, I.; Mari'i, F. M.; Ali, A. A. *J. Heterocycl. Chem.* **1989**, *26*, 1461. (c) Fan, W.-Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: Oxford, 1996; Vol. *4*, pp 1−126. (d) Alvarez, R.; Velazquez, S.; San, F.; Aquaro, S.; De, C.; Perno, C. F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185. (e) Baures, P. W. *Org. Lett.* **1999**, *1*, 249. (f) Palmer, L. M.; Janson, C. A.; Smith, W. W. *PCT Int. Appl.* 2005; p 347. CODEN: PIXXD2 WO 2005016237 A2 20050224, CAN: 142:256748 (patent written in English).

(2) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633. (c) Huisgen, R.; Knorr, R.; Möbius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 4014.

(3) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

(4) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(5) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.

(6) (a) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249. (b) Meldal, M.; Tornø, C. W. *Chem. Rev.* **2008**, 108. (c) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905. (d) Paterson, M. J.; Robb, M. A.; Blancafort, L.; DeBellis, A. D. *J. Am. Chem. Soc.* **2004**, *126*, 2912. (e) Lober, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett.* **2004**, *6*, 1753. (f) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928. (g) Brik, A.; Muldoon, J.; Lin, Y.-C.; Elder, J. H.; Goodsell, D. S.; Olson, A. J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *ChemBioChem* **2003**, *4*, 1246. (h) Lee, L. V.; Mitchell, M. L.; Huang, S.-J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 9588.

(7) (a) Wu, Y. M.; Deng, J.; Li, Y.; Chen, Q. Y. *Synthesis* **2005**, 1314. (b) Nolte, C.; Mayer, P.; Straub, B. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 2101. (c) Kuijpers, B. H. M.; Dijkmans, G. C. T.; Groothuys, S.; Quaedflieg, P. J. L. M.; Blaauw, R. H.; van Delft, F. L.; Rutjes, F. P. J. T. *Synlett* **2005**, 3059. (d) Gerard, B.; Ryan, J.; Beeler, A. B.; Porco, J. A., Jr. *Tetrahedron* **2006**, *62*, 6405. (e) Zhang, X.; Hsung, R. P.; Li, H. *Chem. Commun.* **2007**, 2420. (f) Hein, J. E.; Tripp, J. C.; Krasnova, L.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8018.

(8) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.

(9) Ding, S.; Jia, G.; Sun, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1877.

(10) Barluenga, J.; Valdés, C.; Beltrán, G.; Escribano, M.; Aznar, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 6893.

(11) (a) Ramachary, D. B.; Ramakumar, K.; Narayana, V. V. *Chem.—Eur. J.* **2008**, *14*, 9143. (b) Danence, L. J. T.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. *Chem.—Eur. J.* **2011**, *17*, 3584. (c) Belkheira, M.; Abed, D. E.; Pons, J.-M.; Bressy, C. *Chem.—Eur. J.* **2011**, *17*, 12917.

(12) Thomas, J.; John, J.; Parekh, N.; Dehaen, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 10155.

(13) (a) Sakai, K.; Hida, N.; Kondo, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 179. (b) van Berkel, S. S.; Brauch, S.; Gabriel, L.; Henze, M.; Stark, S.; Vasilev, D.; Wessjohann, L. A.; Abbas, M.; Westermann, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 5343.

(14) Chen, Z.; Yan, Q.; Liu, Z.; Xu, Y.; Zhang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 13324.

(15) Cai, Z.-J.; Wang, S.-Y.; Ji, S.-J. *Org. Lett.* **2013**, *15*, 5226.

(16) Hao, W.-J.; Wang, J.-Q.; Xu, X.-P.; Zhang, S.-L.; Wang, S.-Y.; Ji, S.-J. *J. Org. Chem.* **2013**, *78*, 12362.

(17) Compounds **3g** and **3v** were determined by X-ray crystallography. See the Supporting Information for full details. CCDC 1001829 (**3g**) and 1001828 (**3v**) contain 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.

(18) (a) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Perrulli, F. R.; Santeusanio, S. *Eur. J. Org. Chem.* **2009**, 3109. (b) Rossi, E.; Arcadi, A.; Abbiati, G.; Attanasi, O. A.; Crescentini, L. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1400. (c) Attanasi, O. A.; Favi, G.; Filippone, P.; Giorgi, G.; Mantellini, F.; Moscatelli, G.; Spinelli, D. *Org. Lett.* **2008**, *10*, 1983. (d) Attanasi, O. A.; Favi, G.; Filippone, P.; Mantellini, F.; Moscatelli, G.; Perrulli, F. R. *Org. Lett.* **2010**, *12*, 468. (e) Attanasi, O. A.; Favi, G.; Mantellini, F.; Moscatelli, G.; Santeusanio, S. *Adv. Synth. Catal.* **2011**, *353*, 1519. (f) Chen, J.-R.; Dong, W.-R.; Candy, M.; Pan, F.-F.; Jörres, M.; Bolm, C. *J. Am. Chem. Soc.* **2012**, *134*, 6924. (g) Hatcher, J. M.; Coltart, D. M. *J. Am. Chem. Soc.* **2010**, *132*, 4546. (h) Tong, M.-C.; Chen, X.; Li, J.; Huang, R.; Tao, H.; Wang, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 4680.

(19) (a) Grirrane, A.; Corma, A.; García, H. *Science* **2008**, *322*, 1661. (b) Grirrane, A.; Corma, A.; García, H. *Nat. Protoc.* **2010**, *11*, 429. (c) Takeda, Y.; Okumura, S.; Minakata, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7804. (d) Zhang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 6174. (e) Jonsson, M.; Lind, J.; Eriksen, T. E.; Merényi, G. *J. Am. Chem. Soc.* **1994**, *116*, 1423. (f) Chen, X. Y.; Wang, X. Y.; Sui, Y. X.; Li, Y. Z.; Ma, J.; Zuo, J. L.; Wang, X. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 11878.