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Iron(III) Chloride Catalyzed Nucleophilic Substitution of Tertiary Propargylic Alcohols and Synthesis of Iodo-3*H*-Pyrazoles

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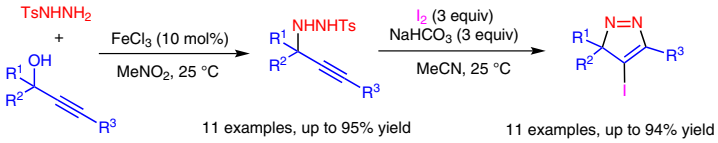

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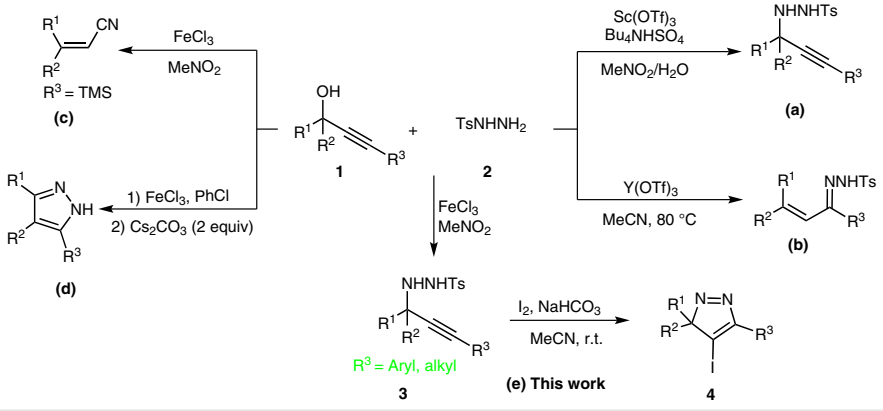
Abstract A straightforward and concise method was developed for the efficient and rapid synthesis of iodo-3*H*-pyrazoles by the $FeCl_3/I_2$-mediated propargylic substitution of tertiary propargylic alcohols with *p*-toluenesulfonyl hydrazide and subsequent cyclization under mild conditions. The method constitutes a novel approach to the synthesis of various iodo-3*H*-pyrazoles with a wide substrate scope and in high yields.

Key words propargylic alcohols, tosyl hydrazide, iodopyrazoles, cyclization, iodination

Transition-metal-catalyzed cascade reactions of propargylic alcohols have received considerable attention, because many complicated molecules can be directly constructed by these reactions from readily accessible starting materials under mild conditions.[1] Among such reactions, Lewis acid catalyzed nucleophilic substitutions of propargylic alcohols with various nucleophiles to achieve carbon–carbon and carbon–heteroatom bond formations have been extensively studied.[2] Nevertheless, compared with the wide range of applications of amine nucleophiles in C–N bond formation, the substitution of propargylic alcohols, particularly tertiary propargylic alcohols, with hydrazines as nucleophiles has rarely been reported,[3] even though propargylic hydrazide products have been converted into useful compounds that contain one or two nitrogen atoms and that exhibit various biological activities.[4] The first convenient method for the preparation of propargylic hydrazides from tertiary propargylic alcohols through scandium-catalyzed hydrazination in $MeNO_2$–H_2O was reported by Yoshimatsu and co-workers in 2012 (Scheme 1, a).[5] However, when tertiary propargylic alcohols were used as substrates, R^3 was limited to a PhS group, and the presence of Bu_4NHSO_4 as an additive was required.

Our group has made great efforts to synthesize heterocycles by using propargylic alcohols as substrates,[6] and we have reported a novel $FeCl_3$-catalyzed domino regioselec-

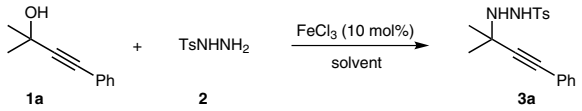


Scheme 1 Reactions of tertiary propargylic alcohols **1** with *p*-toluenesulfonyl hydrazide (**2**)

tive propargylic substitution/aza-Meyer–Schuster rearrangement reaction for the synthesis of acrylonitriles from trimethylsilyl-substituted tertiary propargylic alcohols and *p*-toluenesulfonyl hydrazide (Scheme 1, c).[7] We have also developed a one-pot synthesis of pyrazoles from the same starting materials through a four-step cascade sequence (Scheme 1, d).[8] More recently, Chen and co-workers reported the $Y(OTf)_3$-catalyzed stereoselective synthesis of α,β-unsaturated hydrazones from tertiary propargylic alcohols and *p*-toluenesulfonyl hydrazide (Scheme 1, b).[9] As part of our ongoing efforts to expand the synthetic utility of tertiary propargylic hydrazides, we report a highly efficient $FeCl_3$-catalyzed substitution of tertiary propargylic alcohols to give propargylic hydrazides, and the synthesis of iodo-3*H*-pyrazoles (Scheme 1, e). 3*H*-Pyrazole derivatives are used extensively in syntheses of cyclopropenes, carbene intermediates, and diazoalkenes; they can also undergo rearrangements, cycloadditions, or Diels–Alder reactions.[10] However, approaches to this family of heterocycles usually rely on the cycloaddition of diazo compounds, which always presents danger.[11] To the best of our knowledge, there are few reports on the preparation of iodo-3*H*-pyrazoles or their derivatization.

In our previous studies, we found that $FeCl_3$ is an efficient catalyst for propargylic substitution. To prepare propargyl hydrazides with high efficiency, we screened various solvents and temperatures (Table 1). Initially, the tertiary propargylic alcohol **1a** and *p*-toluenesulfonyl hydrazide (**2**) were treated with $FeCl_3$ (10 mol%) in dichloromethane at room temperature; this gave the target product **3a** in 89% yield (Table 1, entry 1), whereas CH_2Cl_2 at reflux decreased the yield to 50% (entry 2). Changing the solvent to MeCN resulted in an unsatisfactory yield of **3a** (entry 3). To our delight, the reaction in $MeNO_2$ gave a 95% yield of **3a** at room temperature (entry 4); raising the reaction temperature gave lower yields (entries 5 and 6). A test with PhCl as the solvent was unsuccessful (entry 7). In contrast, reducing the amount of $FeCl_3$ to 5 mol% led to a decrease in the yield of **3a** to 84% (entry 8). Therefore, the optimal conditions for this reaction were determined to be $MeNO_2$ as the solvent, at room temperature, with $FeCl_3$ (10 mol%) as the catalyst for about six hours (entry 4).

Table 1 Optimization of Reaction Conditions for the Propargylic Substitution[a]

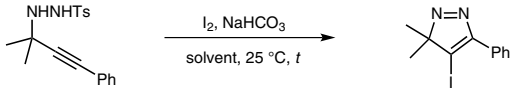


Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	CH_2Cl_2	25	20	89
2	CH_2Cl_2	reflux	2	50
3	MeCN	25	12	75
4	**$MeNO_2$**	**25**	**6**	**95**
5	$MeNO_2$	30	2	90
6	$MeNO_2$	60	0.1	74
7	PhCl	25	24	20
8[c]	$MeNO_2$	25	14	84

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), solvent (5 mL), r.t., in air.
[b] Isolated yield based on **1a**.
[c] $FeCl_3$ (5 mol%).

We next optimized the I_2-mediated synthesis of 4-iodo-3,3-dimethyl-5-phenyl-4,5-dihydro-3*H*-pyrazole (**4a**) from hydrazide **3a** (Table 2). We were pleased to find that the propargyl hydrazide **3a** could be smoothly converted into the pyrazole **4a** by treatment with three equivalents of I_2 and $NaHCO_3$ in MeCN (Table 2, entry 1; 94% yield). Reducing the amounts of catalysts or changing the solvent resulted in unsatisfactory yields (entries 2–5). Therefore, the optimal reaction conditions for the cyclization of propargyl hydrazides are three equivalents of I_2 and $NaHCO_3$ as catalyst and base, respectively, with MeCN as the solvent at room temperature in air (entry 1).

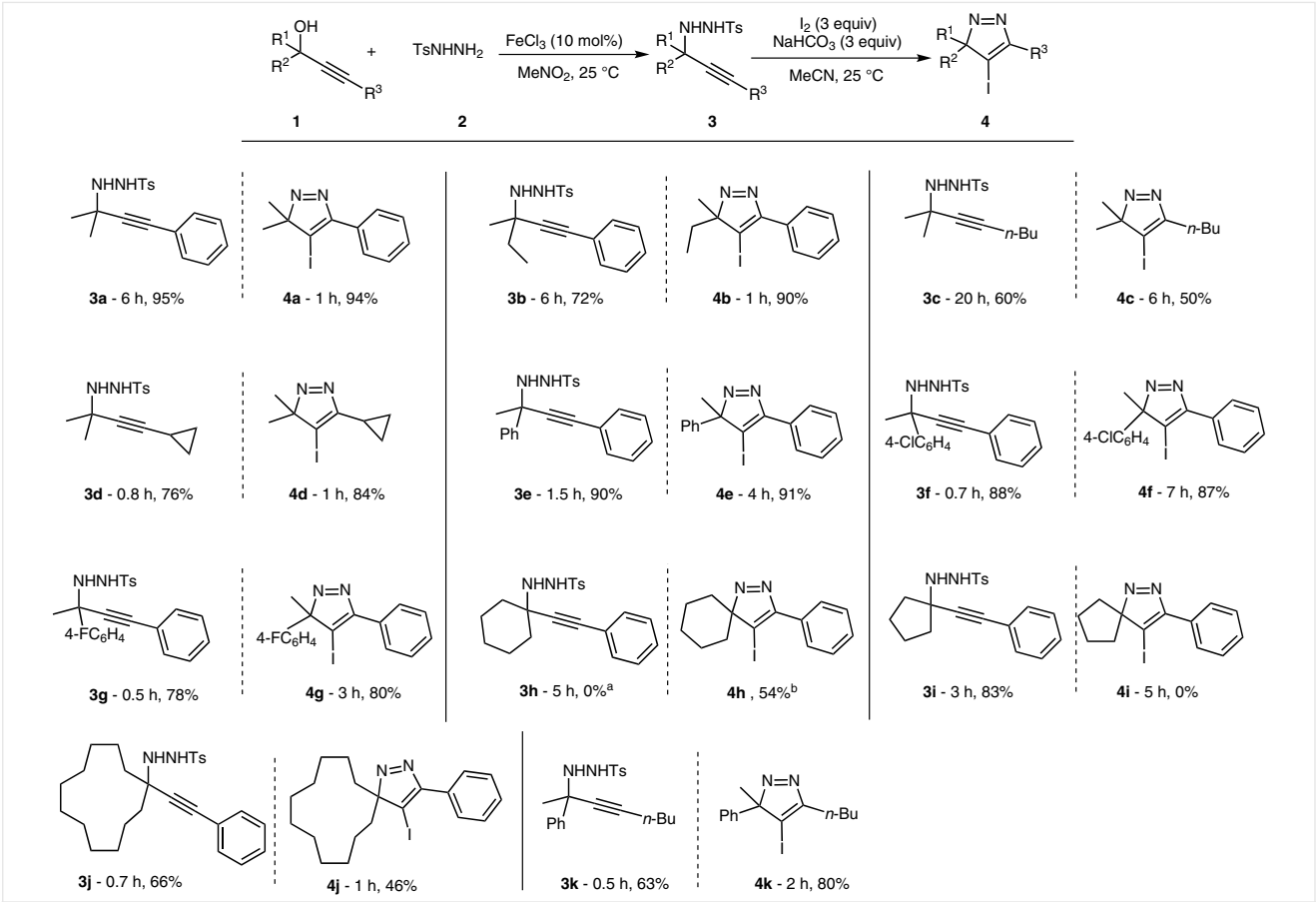
Table 2 Optimization of Reaction Conditions for the I_2-Mediated Cyclization of Propargylic Hydrazide **3a**[a]



Entry	Solvent	I_2 (equiv)	$NaHCO_3$ (equiv)	Time (h)	Yield[b] (%)
1	**MeCN**	**3.0**	**3.0**	**1**	**94**
2	MeCN	2.0	2.0	2	89
3	$MeNO_2$	3.0	3.0	4	88
4	MeOH	3.0	3.0	24	N.R.[c]
5	THF	3.0	3.0	24	N.R.

[a] Reaction conditions: **3a** (0.5 mmol), solvent (5 mL), r.t., in air.
[b] Isolated yield based on **3a**.
[c] No reaction.

Next, we evaluated the scope of the reaction under the optimal conditions by placing various substituents at various positions on the propargylic alcohol **1** (Scheme 2). A variety of propargyl hydrazides **3** and the corresponding iodo-3*H*-pyrazoles **4** were successfully obtained. Propargylic alcohols with a terminal aromatic group (R^3 = Ph) reacted better than did those with an alkyl group (**3a** versus **3c** and **3d**; **4a** versus **4c** and **4d**). In addition, the presence of a long chain at the propargyl position reduced the yield slightly (**3b** and **4b**; 72 and 90% yield, respectively). Substrates with a phenyl and a methyl group in the propargyl position reacted smoothly to afford the desired products (**3e–g**, 78–90% yield; **4e–g**, 80–91% yield). Product **3h** decomposed over the course of column chromatography; however, **4h**

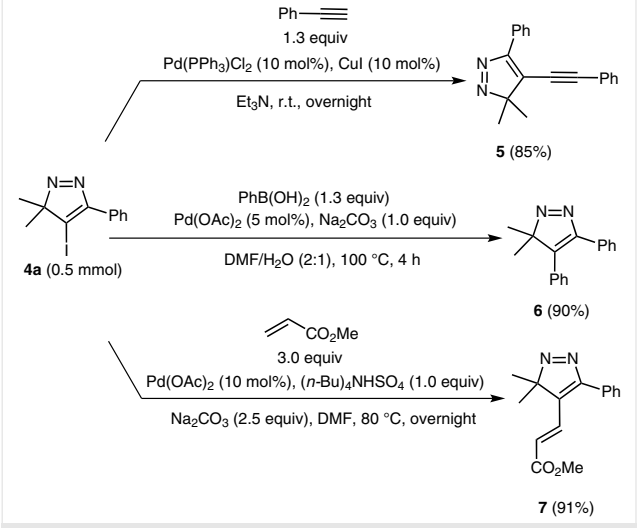


Scheme 2 Synthesis of propargyl hydrazides **3** and the corresponding iodo-3*H*-pyrazoles **4**. *Reagents and conditions*: **1** (0.5 mmol), **2** (0.75 mmol), $FeCl_3$ (10 mol%), $MeNO_2$ (5 mL), r.t., air, then **3** (0.5 mmol), I_2 (1.5 mmol), $NaHCO_3$ (1.5 mmol), MeCN (5 mL), air, 25 °C. [a] **3h** decomposed over the course of column chromatography. [b] **4h** was synthesized in one pot by reacting **1h** and **2** for 12 h; upon completion of the reaction, $MeNO_2$ was removed in vacuo and the crude residue was treated with iodine and $NaHCO_3$ in MeCN.

was obtained in a moderate 54% yield by a one-pot synthesis starting from **1h** and **2**. On replacing a cyclohexyl group with a cyclopentyl group, we obtained **3i** successfully in 83% yield, but this could not be converted into the iodo-3*H*-pyrazole **4i**. Interestingly, the present method was also compatible with a large-ring propargyl alcohol as the substrate, albeit with moderate efficiency (**3j**, 66% yield; **4j**, 46% yield). Replacement of the phenyl group at R^3 in **3e** with a butyl group was also tolerated (**3k**, 63% yield; **4k**, 80% yield).

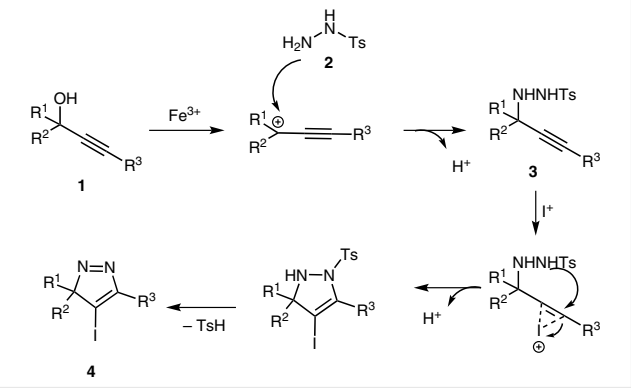
To demonstrate the synthetic utility of this method, derivatization reactions of the iodo-3*H*-pyrazole **4a** were carried out (Scheme 3). Under classic conditions, the Sonogashira, Suzuki, and Heck reactions all proceeded smoothly to give the corresponding products **5**, **6**, and **7** in 85, 90, and 91% yield, respectively.

Based on the experimental results presented above, the reaction mechanism shown Scheme 4 is proposed. First, the propargylic alcohol **1** reacts under iron catalysis to yield a



Scheme 3 Derivatization reactions of the iodo-3*H*-pyrazole **4a**

propargylic cation. Next, propargylic substitution occurs regioselectively by attack on the terminal nitrogen atom ($-NH_2$) of hydrazide **2** to give the substitution product **3**. Coordination of the I^+ catalyst with the alkyne activates the triple bond of **3** to nucleophilic attack by the substituted nitrogen atom of the hydrazide (–NHTs); subsequent elimination of one molecule of 4-toluenesulfonic acid leads to the formation of the final product **4**.



Scheme 4 Plausible reaction mechanism

In conclusion, we have developed a highly efficient method for the synthesis of propargyl hydrazides and their corresponding iodo-3*H*-pyrazoles from tertiary propargylic alcohols and *p*-toluenesulfonyl hydrazide.[12] The reactions are high-yielding with a broad substrate scope and proceed under extremely mild conditions. The present method complements conventional reactions for the preparation of this family of compounds, and has potential applications in medicinal chemistry.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588362.

References and Notes

(1) (a) Hao, L.; Zhan, Z.-P. *Curr. Org. Chem.* **2011**, *15*, 1625. (b) Ding, C.-H.; Hou, X.-L. *Chem. Rev.* **2011**, *111*, 1914. (c) Ljungdahl, N.; Kann, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 642. (d) Detz, R.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2009**, 6263.

(2) (a) Guillena, G.; Ramón, D.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611. (b) Debleds, O.; Gayon, E.; Ostaszuk, E.; Vrancken, E.; Campagne, J.-M. *Chem. Eur. J.* **2010**, *16*, 12207. (c) Kabelka, G. W.; Yao, M.-L. *Curr. Org. Synth.* **2008**, *5*, 28. (d) Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501. (e) Wang, X.; Li, S.-y.; Pan, Y.-m.; Wang, H.-s.; Liang, H.; Chen, Z.-f.; Qin, X.-h. *Org. Lett.* **2014**, *16*, 580. (f) Zhu, Y.; Yin, G.; Hong, D.; Lu, P.; Wang, Y. *Org. Lett.* **2011**, *13*, 1024. (g) Bauer, E. I. *Synthesis* **2012**, *44*, 1131. (h) Yin, G.; Zhu, Y.; Zhang, L.; Lu, P.; Wang, Y. *Org. Lett.* **2011**, *13*, 940. (i) Chatterjee, P.; Roy, S. *J. Org. Chem.* **2010**, *75*, 4413. (j) Yan, W.; Wang, Q.; Chen, Y.; Petersen, J.; Shi, X. *Org. Lett.* **2010**, *12*, 3308. (k) Fang, Z.; Liu, J.; Liu, Q.; Bi, X. *Angew. Chem. Int. Ed.* **2014**, *53*, 7209. (l) Yoshimatsu, M.; Watanabe, H.; Koketsu, E. *Org. Lett.* **2010**, *12*, 4192. (m) Fang, C.; Pang, Y.; Forsyth, C. *Org. Lett.* **2010**, *12*, 4528. (n) Sanz, R.; Miguel, D.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Org. Lett.* **2007**, *9*, 727. (o) Zhan, Z.-p.; Yang, W.-z.; Yang, R.-f.; Yu, J.-l.; Li, J.-p.; Liu, H.-j. *Chem. Commun.* **2006**, 3352.

(3) For selected examples of the use of secondary propargyl alcohols and hydrazines as nucleophiles, see: (a) Xu, S.-X.; Hao, L.; Wang, T.; Ding, Z.-C.; Zhan, Z.-P. *Org. Biomol. Chem.* **2013**, *11*, 294. (b) Reddy, C.; Vijaykumar, J.; Grée, R. *Synthesis* **2013**, *45*, 830.

(4) (a) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. In *Targets in Heterocyclic Systems: Chemistry and Properties*; Vol. 6; Attanasi, O. A.; Spinelli, D., Eds.; RSC: Cambridge, **2002**, 52. (b) Kiyokawa, K.; Ito, Y.; Kakehi, R.; Ogawa, T.; Goto, Y.; Yoshimatsu, M. *Eur. J. Org. Chem.* **2016**, 4998.

(5) Yoshimatsu, M.; Ohta, K.; Takahashi, N. *Chem. Eur. J.* **2012**, *18*, 15602.

(6) (a) Wen, J.-J.; Zhu, Y.; Zhan, Z.-P. *Asian J. Org. Chem.* **2012**, *1*, 108. (b) Wang, T.; Chen, X.-l.; Chen, L.; Zhan, Z.-p. *Org. Lett.* **2011**, *13*, 3324. (c) Liu, X.-t.; Huang, L.; Zheng, F.-j.; Zhan, Z.-p. *Adv. Synth. Catal.* **2008**, *350*, 2778. (d) Pan, Y.-m.; Zheng, F.-j.; Lin, H.-x.; Zhan, Z.-p. *J. Org. Chem.* **2009**, *74*, 3148. (e) Gao, X.; Pan, Y.-m.; Lin, M.; Chen, L.; Zhan, Z.-p. *Org. Biomol. Chem.* **2010**, *8*, 3259. (f) Hao, L.; Pan, Y.; Wang, T.; Lin, M.; Chen, L.; Zhan, Z.-p. *Adv. Synth. Catal.* **2010**, *352*, 3215. (g) Zhan, Z.-p.; Yu, J.-l.; Liu, H.-j.; Cui, Y.-y.; Yang, R.-f.; Yang, W-z.; Li, J.-p. *J. Org. Chem.* **2006**, *71*, 8298.

(7) Hao, L.; Wu, F.; Ding, Z.-C.; Xu, S.-X.; Ma, Y.-L.; Chen, L.; Zhan, Z.-p. *Chem. Eur. J.* **2012**, *18*, 6453.

(8) Hao, L.; Hong, J.-J.; Zhu, J.; Zhan, Z.-p. *Chem. Eur. J.* **2013**, *19*, 5715.

(9) Liu, W.; Wang, H.; Zhao, H.; Li, B.; Chen, S. *Synlett* **2015**, *26*, 2170.

(10) (a) Closs, G. L.; Boll, W. A. *J. Am. Chem. Soc.* **1963**, *85*, 3904. (b) Hamdi, N.; Dixneuf, P. H.; Arfaoui, Y.; Haloui, E. *J. Chem. Res.* **2005**, 289. (c) Hamdi, N.; Lachheb, J.; Msaddek, M. *J. Soc. Alger. Chim.* **2007**, *17*, 37. (d) Anet, R.; Anet, F. A. L. *J. Am. Chem. Soc.* **1964**, *86*, 525. (e) Padwa, A.; Wannamaker, M. W.; Dyszlewski, A. D. *J. Org. Chem.* **1987**, *52*, 4760. (f) Mataka, S.; Ohshima, T.; Tashiro, M. *J. Org. Chem.* **1981**, *46*, 3960. (g) Jefferson, E. A.; Warkentin, J. *J. Org. Chem.* **1994**, *59*, 455. (h) Franck-Neumann, M. *Angew. Chem. Int. Ed.* **1967**, *6*, 79. (i) Rigby, J. H.; Kierkus, P. C. *J. Am. Chem. Soc.* **1989**, *111*, 4125. (j) Merchant, R. R.; Allwood, D. M.; Blakemore, D. C.; Ley, S. V. *J. Org. Chem.* **2014**, *79*, 8800.

(11) (a) Moritani, I.; Hosokawa, T.; Obata, N. *J. Org. Chem.* **1969**, *34*, 670. (b) Wenkert, E.; McPherson, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 8084. (c) Pyron, R. S.; Jones, W. M. *J. Org. Chem.* **1967**, *32*, 4048. (d) Zimmerman, H. E.; Hovey, M. C. *J. Org. Chem.* **1979**, *44*, 2331.

(12) ***N'*-(1,1-Dimethyl-3-phenylprop-2-yn-1-yl)-4-toluenesulfonohydrazide (3a); Typical Procedure**
$TsNHNH_2$ (**2**; 129.5mg, 0.75 mmol), propargylic alcohol **1a** (80 mg, 0.5 mmol), and $FeCl_3$ (8.1 mg, 0.05 mmol) were added to a 10 mL round-bottomed flask. $MeNO_2$ (5 mL) was added, and the mixture was stirred in air at r.t. until the reaction was complete (TLC). The solvent was removed under vacuum, and the crude

residue was purified by column chromatography on silica gel to give a white solid; yield: 156 mg (95%); mp 117–119 °C. IR (film): 3461, 3130, 2180, 1598, 1499 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 6 H), 2.41 (s, 3 H), 3.67 (s, 1 H), 6.15 (s, 1 H), 7.26–7.38 (m, 7 H), 7.82 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (100 MHz, CDCl3): δ = 21.5, 27.0, 53.2, 83.3, 91.7, 122.4, 128.2, 128.3, 128.3, 129.3, 131.7, 135.3, 143.8. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{21}N_2O_2S$: 329.1318; found: 329.1320.

4-Iodo-3,3-dimethyl-5-phenyl-3*H*-pyrazole (4a)

Propargyl hydrazide **3a** (164 mg, 0.5 mmol), I_2 (381 mg, 1.5 mmol), and $NaHCO_3$ (126 mg, 1.5 mmol) were added to a 10 mL round-bottomed flask. MeCN (5 mL) was added, and the mixture was stirred at r.t. in air until the reaction was complete (TLC). Sat. aq $Na_2S_2O_3$ was added to quench the reaction, and the mixture was diluted with H_2O (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed under vacuum, and the crude residue was purified by column chromatography (silica gel) to give a yellow solid; yield: 140 mg (94%); mp 138–140 °C. IR (film): 3102, 1597, 1489 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 6 H), 7.47–7.53 (m, 3 H), 8.26–8.28 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 97.5, 111.3, 128.2, 128.5, 129.5, 130.6, 154.0. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{12}IN_2$: 299.0040; found: 299.0042.