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SHORT COMMUNICATION

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Facile Access to 1*H*-Indazoles through Iodobenzene-Catalyzed C–H Amination under Mild, Transition-Metal-Free Conditions

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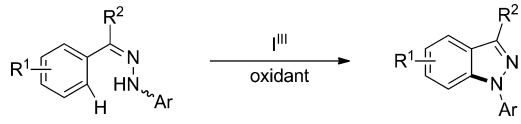
The transition-metal- and halogen-free synthesis of *N*-aryl-substituted 1*H*-indazole and derivatives was accomplished on the basis of the iodobenzene-catalyzed intramolecular C–H amination of hydrazones under mild conditions. Reactions of hydrazones derived from ketones and hydrazines with a catalytic amount of iodobenzene in the presence of Oxone as an oxidant in trifluoroacetic acid took place to afford 1*H*-indazoles in moderate to good yields. A plausible reaction mechanism was described on the basis of the control experiments.

Introduction

1*H*-Indazole and its derivatives are known to be important structural units for the development of pharmaceutically important molecules.[1] For instance, they present antiarthritic,[2] anti-inflammatory,[3] and antifertility activities.[4] Traditional syntheses of 1*H*-indazoles often require harsh reaction conditions, toxic reagents, and unstable intermediates, all of which have restricted their substrate scope and their industrial application.[5] Recently, the transition-metal-catalyzed synthesis of 1*H*-indazoles was documented on the basis of intramolecular Buchwald–Hartwig-type coupling reactions and/or C–H amination.[6] Although these methods are effective under milder reaction conditions than those required for the traditional synthesis,[5] the high cost and toxicity of the transition metals restrict their practical use. Accordingly, the development of a new protocol for the formation of 1*H*-indazole scaffolds under transition-metal-free conditions is highly desirable.[7]

Recently, the use of hypervalent iodine reagents in oxidative reactions as metal-free reagents has received much attention owing to their low toxicity and the fact that they can be used under mild reaction conditions.[8] Many useful carbon–carbon[9] and carbon–heteroatom[10] bond-forming reactions have been documented in which a stoichiometric amount of the hypervalent iodine reagent is used. More recently, a catalytic process involving the use of *m*-chloroperoxybenzoic acid (*m*CPBA) as a terminal oxidant to avoid the formation of undesired iodoarenes in an equimolar amount was reported.[11] On the basis of this concept, a variety of methods have been developed for the transformation of organic molecules.[12] We now report iodobenzene-catalyzed oxidative C–H amination for the construction of 1*H*-indazoles from arylhydrazones by using Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as a terminal oxidant under mild reaction conditions (Scheme 1).



Scheme 1. Synthesis of 1*H*-indazoles from hydrazones.

Results and Discussion

The reaction conditions were optimized by using phenylhydrazone **1a** as a model substrate (Table 1). Treatment of **1a** with iodobenzene (30 mol-%) and *m*CPBA (1.5 equiv.) as the oxidant in hexafluoroisopropanol (HFIP, 2 mL) as the solvent for 24 h at room temperature afforded target 1*H*-indazole **2a** in 9% yield (Table 1, Entry 1). Screening of the solvents, including trifluoroethanol (TFE), toluene, dichloromethane, methanol, acetic acid, and DMSO, proved unsuccessful (Table 1, Entries 2–7). Fortunately, target **2a** was obtained in 48% yield by using trifluoroacetic acid (TFA) as the solvent (Table 1, Entry 8). Employing other substituted iodoarenes, such as *p*-iodotoluene and *p*-iodoanisole, and also iodine sources, such as iodine and tetrabutylammonium iodide, produced inferior results (Table 1, Entries 9–12). Additionally, reactions performed with oxidants such as *tert*-butyl hydroperoxide (TBHP), hydrogen peroxide, and potassium persulfate were unsuccessful (Table 1, Entries 13–15). To our delight, upon employing Oxone (potassium peroxymonosulfate) as the oxidant, **2a** was obtained in 41% yield (Table 1, Entry 16). Lowering the temperature to –10 °C led to isolation of the product in 90% yield (Table 1, Entry 18). Fortunately, low-

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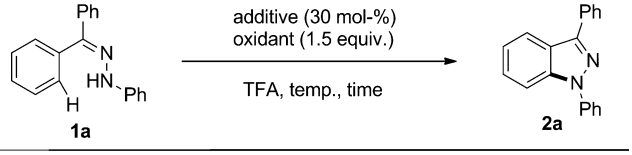
ering the quantity of iodobenzene from 30 to 10 mol-% led to an acceptable yield of the product (84%; Table 1, Entry 19). Control experiments without the use of iodobenzene and Oxone afforded **2a** in 16 and 0% yield, respectively (Table 1, Entries 20 and 21).

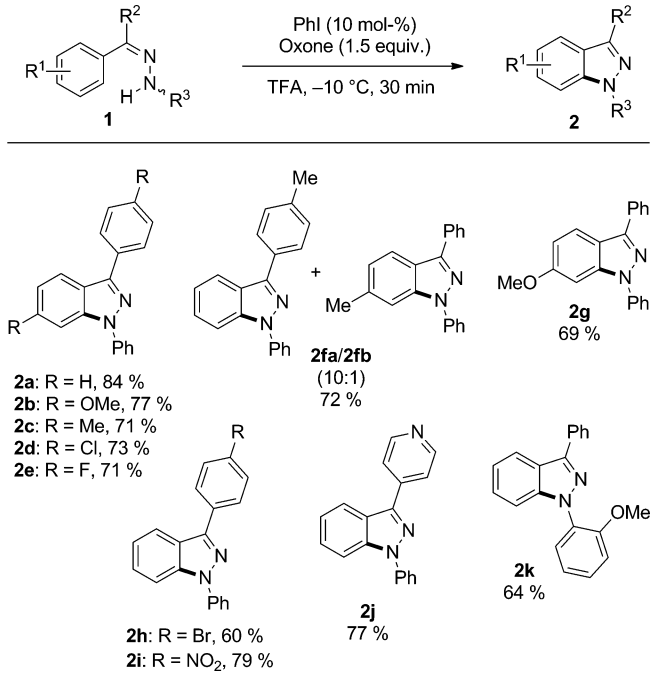
Table 1. Optimization of the reaction conditions for the cyclization of phenylhydrazone **1a**.[a]



Entry	Oxidant	Additive	Solvent	T [°C]	t [h]	Yield[b] [%]
1	*m*CPBA	PhI	HFIP	r.t.	24	9
2	*m*CPBA	PhI	TFE	r.t.	24	trace
3	*m*CPBA	PhI	toluene	r.t.	24	0
4	*m*CPBA	PhI	CH_2Cl_2	r.t.	24	0
5	*m*CPBA	PhI	MeOH	r.t.	12	0
6	*m*CPBA	PhI	AcOH	r.t.	12	0
7	*m*CPBA	PhI	DMSO	r.t.	12	0
8	*m*CPBA	PhI	TFA	r.t.	12	48
9	*m*CPBA	*p*-MeC_6H_4I	TFA	r.t.	6	20
10	*m*CPBA	*p*-$MeOC_6H_4I$	TFA	r.t.	6	16
11	*m*CPBA	I_2	TFA	r.t.	6	trace
12	*m*CPBA	Bu_4NI	TFA	r.t.	6	trace
13	70% aq. TBHP	PhI	TFA	r.t.	6	0
14	30% H_2O_2	PhI	TFA	r.t.	6	0
15	$K_2S_2O_8$	PhI	TFA	r.t.	6	0
16	Oxone	PhI	TFA	r.t.	6	41
17	Oxone	PhI	TFA	0	0.5	81
18	Oxone	PhI	TFA	–10	0.5	90
19[c]	Oxone	PhI	TFA	–10	0.5	84
20	Oxone	–	TFA	–10	0.5	16
21	–	PhI	TFA	–10	0.5	0

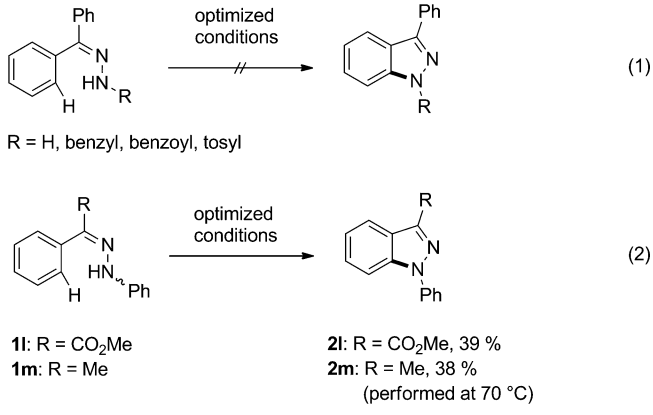
[a] The reaction was performed with the iodine compound (0.3 equiv.) and oxidant (1.5 equiv.) unless otherwise stated. [b] The yield of **2a** after flash chromatography. [c] The reaction was performed with 10 mol-% of the additive.

With the optimized conditions in hand, we next investigated the scope of the cyclization of a series of substituted hydrazones (Scheme 2). Hydrazones **1b** and **1c** with methoxy and methyl substituents on both benzene rings reacted to give corresponding substituted 1*H*-indazoles **2b** and **2c** in 77 and 71% yield, respectively. Substrates **1d** and **1e** bearing halogen substituents also gave target products **2d** and **2e** in 73 and 71% yield, respectively. As can be anticipated, the substrate singly substituted with a methyl group provided a mixture of regioisomeric products **2fa** and **2fb**. Interestingly, if phenylhydrazone **1g** with a methoxy group was employed as the substrate, the reaction proceeded with high regioselectivity to afford **2g** throughout the cyclization from the electron-rich benzene ring. However, cyclization of bromo- and nitro-substituted pyridine-ring-containing substrates **1h**, **1i**, and **1j** preferentially occurred from the electron-rich benzene ring to afford **2h**, **2i**, and **2j**. Substrate **1k** with a substituent at the hydrazine-derived benzene ring also underwent cyclization to afford 1*H*-indazole **2k** in moderate yield.



Scheme 2. Scope of the cyclization of hydrazones. Yields of the products obtained after chromatography are given.

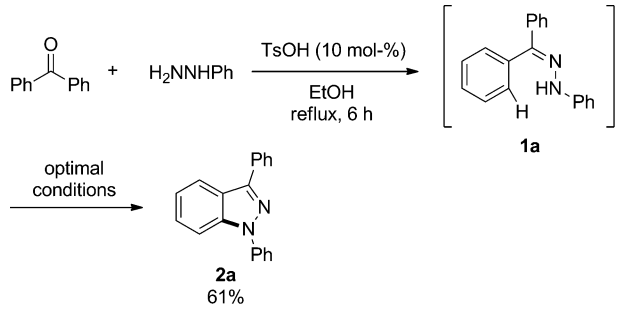
Disappointingly, transformation of hydrazones with benzyl, benzoyl, and *p*-toluenesulfonyl groups and transformation of a hydrazone without any substituents at the terminal nitrogen atom could not be achieved under the optimized conditions; the starting materials were recovered, and this could partially be attributed to the instability of the nitrenium ion [Scheme 3, Equation (1)].[12b] Also, reaction of hydrazones **1l** and **1m** with methoxycarbonyl and methyl groups instead of the aryl group afforded poor yields of corresponding indazoles **2l** and **2m** [Scheme 3, Equation (2)].



Scheme 3. Unsuccessful and inefficient transformations.

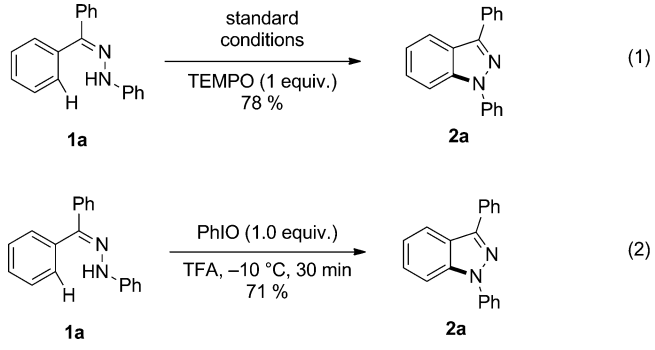
A one-pot process without the isolation of hydrazone intermediate **1a** was achieved by using benzophenone and phenylhydrazine as the starting materials (Scheme 4). The reaction of both starting materials in the presence of an

acid catalyst afforded hydrazone **1a**, which was treated with iodobenzene and Oxone under the optimal conditions to provide target indazole **2a** in 61% yield.



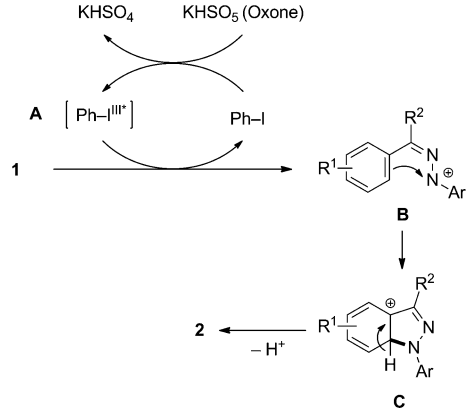
Scheme 4. The one-pot synthesis of 1*H*-indazole **2a**. TsOH = *p*-toluenesulfonic acid.

To obtain information about the reaction mechanism, we next investigated the following control experiments. The reaction of **1a** was not suppressed if TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl), a radical-trapping reagent, was added [Scheme 5, Equation (1)]. As expected, the reaction with PhIO afforded product **2a** in almost the same efficiency [Scheme 5, Equation (2)].



Scheme 5. Control experiments.

A plausible catalytic cycle for this transformation is shown in Scheme 6.[12b] The oxidation of iodobenzene by Oxone affords hypervalent iodine(III) species **A**, which reacts with hydrazone **1** to form nitrenium ion intermediate **B**. Intramolecular nucleophilic substitution provides indazole **2** via carbocation **C**. The liberated iodobenzene is reoxidized to **A** by Oxone.



Scheme 6. Plausible catalytic cycle.

Conclusions

We achieved the facile synthesis of multisubstituted 1*H*-indazoles with an *N*-aryl substituent from readily available hydrazones on the basis of iodobenzene-catalyzed oxidative C–H aminations by using Oxone as a stable and inexpensive oxidant under mild conditions within a short reaction time. The scope and limitations of this transformation and also valuable information with regard to the reaction mechanism were partially elucidated (Schemes 3–5). This transformation avoids the use of a toxic transition-metal catalyst and leaving groups, which require additional steps for pre-functionalization. A range of functional groups [methoxy, methyl, halogen (Br, Cl, and F), ester, and 4-pyridyl] were accepted for this transformation to provide a series of functionalized 1*H*-indazoles in moderate to good yields.

Experimental Section

General Procedure: Oxone (0.60 mmol, 1.5 equiv.) was added to a stirred solution of hydrazone **1** (0.40 mmol, 1.0 equiv.) and iodobenzene (10 mol-%) in TFA (2 mL) at –10 °C. The mixture was stirred for 30 min and then quenched with water, diluted with $CHCl_3$, and washed with water (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate) to afford pure substituted 1*H*-indazole **2**.

Supporting Information (see footnote on the first page of this article): Experimental procedures, complete characterization data of all the new compounds, and copies of the ^{1}H NMR and ^{13}C NMR spectra.

Acknowledgments

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[1] N. A. S. Ali, B. A. Dar, V. Pradhan, M. Farooqui, *Mini-Rev. Med. Chem.* **2013**, *13*, 1792.
[2] G. A. Bistocchi, G. D. Meo, M. Pedini, A. Ricci, H. Brouilhet, S. Boucherie, M. Rabaud, P. Jacquignon, *Farmaco, Ed. Sci.* **1981**, *36*, 315.
[3] L. Mosti, L. Sansebastiano, P. Fossa, P. Schenone, F. Mattioli, *Farmaco* **1992**, *47*, 357.
[4] D. A. Buthala, T. J. Lobl, *Cytobios* **1979**, *25*, 23.
[5] For a review, see: A. Schmidt, A. Beutler, B. Snovydovych, *Eur. J. Org. Chem.* **2008**, 4073.
[6] For palladium catalysis, see: a) J. J. Song, N. K. Yee, *Org. Lett.* **2000**, *2*, 519; b) J. J. Song, N. K. Yee, *Tetrahedron Lett.* **2001**, *42*, 2937; c) C. S. Cho, D. K. Lim, N. H. Heo, T.-J. Kim, S. C. Shim, *Chem. Commun.* **2004**, 104; d) K. Inamoto, M. Katsuno, T. Yoshino, I. Suzuki, K. Hiroya, T. Sakamoto, *Chem. Lett.* **2004**, *33*, 1026; e) K. Inamoto, M. Katsuno, T. Yoshino, Y. Arai, K. Hiroya, T. Sakamoto, *Tetrahedron* **2007**, *63*, 2695; f) K. Inamoto, T. Saito, M. Katsuno, T. Sakamoto, K. Hiroya, *Org. Lett.* **2007**, *9*, 2931; for copper catalysis, see: g) D. Viña,

E. del Olmo, J. L. López-Pérez, A. San Feliciano, *Org. Lett.* **2007**, *9*, 525; h) X. Xiong, Y. Jiang, D. Ma, *Org. Lett.* **2012**, *14*, 2552; i) T. Kylmälä, S. Udd, J. Tois, R. Franzén, *Tetrahedron Lett.* **2010**, *51*, 3613; j) X. Li, L. He, H. Chen, W. Wu, H. Jiang, *J. Org. Chem.* **2013**, *78*, 3636; for iron catalysis, see: k) D. K. O'Dell, K. M. Nicholas, *Heterocycles* **2004**, *63*, 373; l) B. J. Stokes, C. V. Vogel, L. K. Urnezis, M. Pan, T. G. Driver, *Org. Lett.* **2010**, *12*, 2884; m) T. Zhang, W. Bao, *J. Org. Chem.* **2013**, *78*, 1317; for rhodium catalysis, see: n) D.-G. Yu, M. Suri, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 8802.

[7] Recently, the base-catalyzed synthesis of substituted indazoles under mild, transition-metal-free conditions was developed: I. Thomé, C. Besson, T. Kleine, C. Bolm, *Angew. Chem. Int. Ed.* **2013**, *52*, 7509; *Angew. Chem.* **2013**, *125*, 7657.

[8] For some recent reviews, see: a) M. Ochiai, K. Miyamoto, *Eur. J. Org. Chem.* **2008**, 4229; b) T. Dohi, Y. Kita, *Chem. Commun.* **2009**, 2073; c) I. Tellitu, E. Domínguez, *Trends Heterocycl. Chem.* **2011**, *15*, 23; d) E. A. Merritt, B. Olofsson, *Synthesis* **2011**, 517; e) M. Brown, U. Farid, T. Wirth, *Synlett* **2013**, *24*, 424; f) V. V. Zhdankin, *Hypervalent Iodine Chemistry*, Wiley, Chichester, **2014**; g) F. V. Singh, T. Wirth, *Chem. Asian J.* **2014**, *9*, 950.

[9] a) R. Samanta, J. Lategahn, A. P. Antonchick, *Chem. Commun.* **2012**, *48*, 3194; b) J. Wang, Y. Yuan, R. Xiong, D. Zhang-Negrerie, Y. Du, K. Zhao, *Org. Lett.* **2012**, *14*, 2210; c) Y. Gu, D. Wang, *Tetrahedron Lett.* **2010**, *51*, 2004.

[10] a) J. A. Souto, C. Martínez, I. Velilla, K. Muñiz, *Angew. Chem. Int. Ed.* **2013**, *52*, 1324; *Angew. Chem.* **2013**, *125*, 1363; b) U. Farid, T. Wirth, *Angew. Chem. Int. Ed.* **2012**, *51*, 3462; *Angew. Chem.* **2012**, *124*, 3518; c) J. A. Souto, P. Becker, A. Iglesias, K. Muñiz, *J. Am. Chem. Soc.* **2012**, *134*, 15505; d) J. A. Souto, D. Zian, K. Muñiz, *J. Am. Chem. Soc.* **2012**, *134*, 7242; e) Y. Zheng, X. Li, C. Ren, D. Zhang-Negrerie, Y. Du, K. Zhao, *J. Org. Chem.* **2012**, *77*, 10353; f) Y.-B. Kang, L. H. Gade, *J. Org. Chem.* **2012**, *77*, 1610; g) Z. Yu, L. Ma, W. Yu, *Synlett* **2012**, *23*, 1534; h) R. Samanta, J. O. Bauer, C. Strohmann, A. P. Antonchick, *Org. Lett.* **2012**, *14*, 5518; i) W. Zhong, S. Liu, J. Yang, X. Meng, Z. Li, *Org. Lett.* **2012**, *14*, 3336; j) H. J. Kim, S. H. Cho, S. Chang, *Org. Lett.* **2012**, *14*, 1424; k) X. Ban, Y. Pan, Y. Lin, S. Wang, Y. Du, K. Zhao, *Org. Biomol. Chem.* **2012**, *10*, 3606; l) A. Lishchynskyi, K. Muñiz, *Chem. Eur. J.* **2012**, *18*, 2212; m) J. A. Souto, Y. González, A. Iglesias, D. Zian, A. Lishchynskyi, K. Muñiz, *Chem. Asian J.* **2012**, *7*, 1103; n) H. Liu, X. Wang, Y. Gu, *Org. Biomol. Chem.* **2011**, *9*, 1614; o) Y.-B. Kang, L. H. Gade, *J. Am. Chem. Soc.* **2011**, *133*, 3658; p) W. Zhong, J. Yang, X. Meng, Z. Li, *J. Org. Chem.* **2011**, *76*, 9997; q) M. Fujita, M. Wakita, T. Sugimura, *Chem. Commun.* **2011**, *47*, 3983; r) A. A. Kantak, S. Potavathri, R. A. Barham, K. M. Romano, B. Deboef, *J. Am. Chem. Soc.* **2011**, *133*, 19960; s) C. Röben, J. A. Souto, Y. González, A. Lishchynskyi, K. Muñiz, *Angew. Chem. Int. Ed.* **2011**, *50*, 9478; *Angew. Chem.* **2011**, *123*, 9650; t) A. Yoshimura, V. N. Nemykin, V. V. Zhdankin, *Chem. Eur. J.* **2011**, *17*, 10538.

[11] a) M. Ochiai, Y. Takeuchi, T. Katayama, T. Sueda, K. Miyamoto, *J. Am. Chem. Soc.* **2005**, *127*, 12244; b) T. Dohi, A. Maruyama, M. Yoshimura, K. Morimoto, H. Tohma, Y. Kita, *Angew. Chem. Int. Ed.* **2005**, *44*, 6193; *Angew. Chem.* **2005**, *117*, 6349.

[12] a) M. Ito, H. Kubo, I. Itani, K. Morimoto, T. Dohi, Y. Kita, *J. Am. Chem. Soc.* **2013**, *135*, 14078; b) S. K. Alla, R. K. Kumar, P. Sadhu, T. Punniyamurthy, *Org. Lett.* **2013**, *15*, 1334; c) M. Ngatimin, R. Frey, C. Andrews, D. W. Lupton, O. E. Hutt, *Chem. Commun.* **2011**, *47*, 11778; d) V. V. Zhdankin, *J. Org. Chem.* **2011**, *76*, 1185; e) T. Dohi, T. Nakae, Y. Ishikado, D. Kato, Y. Kita, *Org. Biomol. Chem.* **2011**, *9*, 6899; f) A. P. Antonchick, R. Samanta, K. Kulikov, J. Lategahn, *Angew. Chem. Int. Ed.* **2011**, *50*, 8605; *Angew. Chem.* **2011**, *123*, 8764; g) T. Dohi, N. Takenaga, K.-I. Fukushima, T. Uchiyama, D. Kato, M. Shiro, H. Fujioka, Y. Kita, *Chem. Commun.* **2010**, *46*, 7697.

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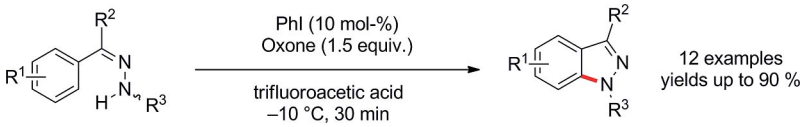

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