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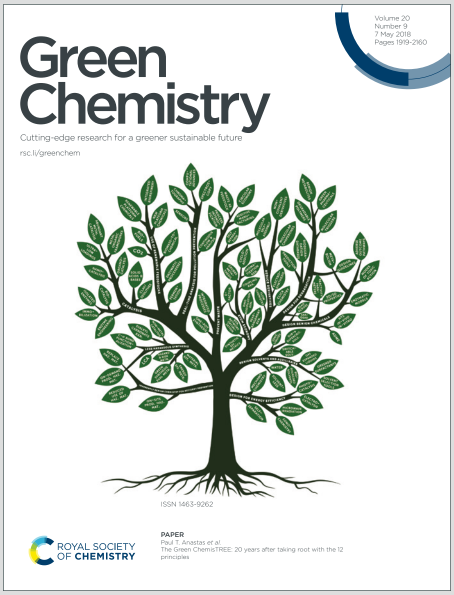

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Synthesis of spiro[2,3-dihydrofuran-3,3′-oxindole] via a multi-component cascade reaction of α-diazo esters, water, isatins and malononitrile/ethyl cyanoacetate

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We reported a green synthesis of spiro[2,3-dihydrofuran-3,3′-oxindole] derivatives which are of potential value in medicinal chemistry. We are able to access the spiro[2,3-dihydrofuran-3,3′-oxindole] derivatives via a $Cu(OTf)_2$-catalyzed or $Cu(OTf)_2/Rh_2(OAc)_4$-cocatalyzed multi-component cascade reaction of *α*-diazo ester, water, isatins and malononitrile/ethyl cyanoacetate. The reaction can be accomplished in good to excellent yields (60-99%) and the structure of products 6a and 6k were supported by X-ray crystallography. The catalyst $Cu(OTf)_2$ can be recycled 4 times without a sharp loss of the yield of 6a. 6q can be easily synthesized in gram-scale. Shortly, the reaction is characterized with step-economy, harmless solvent, and recyclable catalyst.

Green chemical process requires chemists to produce valuable chemicals with least amount of energy, time, and waste.[1] Multi-component reactions (MCR), which arrange the majority of atoms from more than two starting materials into the final product in a single step without releasing pollutant, are an ideal strategy for green chemistry.[2] MCR are known to possess the following features:[2d] 1) MCR are designed to maximize the incorporation of all starting materials into the final product; 2) MCR are designed to access the final product in fewest number of steps; 3) MCR furnish products with structural complexity and diversity via combinatorial method. Therefore, development of novel MCR is one of the efficient methods of fulfilling principles of green chemistry. Furthermore, for the sake of environment, MCR with mild and harmless conditions are highly recommended. Practically, environmentally detrimental solvents like halogenated solvents should be replaced with more favourable solvents such as H_2O, alcohols, esters, etc. On the other hand, recycling the materials of MCR is expected to reduce cost and waste. We are guided by these principles to design reactions to generate functionally interesting molecules.

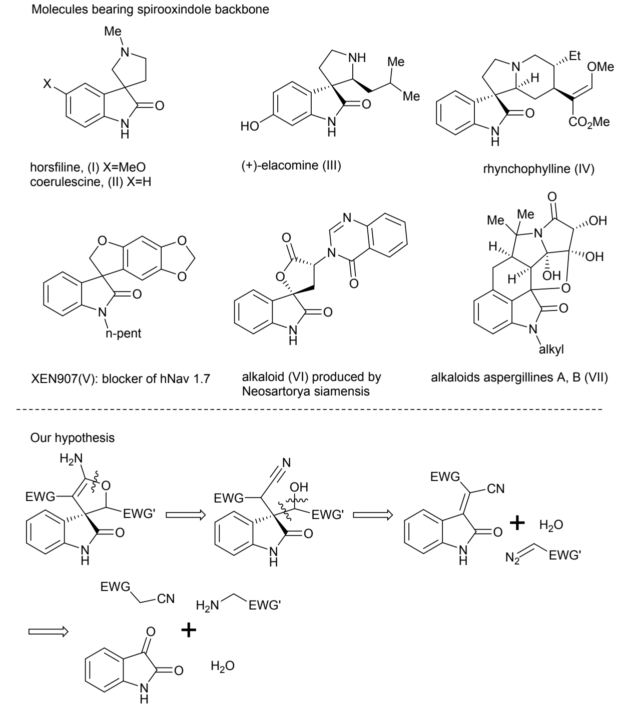

Fig. 1 Biologically active compounds bearing spirooxindole scaffold (top) and our hypothesis of synthesizing spirooxindole (bottom).

Spirooxindole scaffold is widely found in natural products and pharmaceutical molecules.[3] For example, coerulescine (II), (+)-elacomine (III), rhynchophylline (IV), alkaloids (VI) produced by Neosartorya siamensis and alkaloids aspergillines A, B (VII) are natural products with interesting bioactivities.[4] Horsfiline (I) and XEN907 (V) identified as analgesic and inhibitor of hNa1.7 are promising drug candidates (Fig. 1, top).[5] Due to their biological significance, spirooxindole building block has triggered wide interest in organic synthesis community.[6] In recent years, our group and others have documented multi-component reactions using isatin as the one

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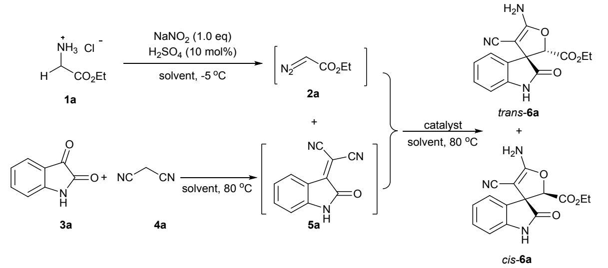
of the starting materials.[7] But a straightforward approach to generating spirooxindoles from isatin remains rare.[8] We envision a multi-component cascade reaction, in which isatylidene malononitrile/2-cyanoacetate is employed to trap the protic oxonium ylide and subsequently undergo intramolecular cyclization, affording spirooxindole in one pot (Fig. 1, bottom). The method represents one of the examples that use environmentally friendly solvents and recycle the material of the reaction, shedding the light upon the green chemistry-oriented reaction development.

At the outset, we conducted the $Rh_2(OAc)_4$-catalyzed multi-component reaction of *in situ*-generated ethyl diazoacetate (EDA) (**2a**) from **glycine ethyl ester hydrochloride (1a),** water and *in situ*-generated **isatylidene malononitrile (5a) from isatin (3a) and** malononitrile (**4a**) in the two-phase solvent of water and dichloromethane (DCM). As depicted in Fig. 1 bottom, Michael-type adduct of hydroxyl oxonium ylide and the isatylidene malononitrile underwent intramolecular ring-closure smoothly to afford **6a** as the final product in 87% yield with 50:50 diastereoselectivity (Table 1, entry 1). Then the reaction was set as the template to screen a series of other metal catalysts. All the catalysts could furnish **6a** in high to excellent yields (81-96%, Table 1, entries 2-8) with 50:50 *dr* values, except Fe $(ClO_4)_3 \cdot xH_2O$ and $Cu(ClO_4)_2 \cdot xH_2O$ (Table 1, entries 9-10), $Cu(OTf)_2$ was the optimal catalyst affording **6a** in 96% yield (Table 1, entry 6).

Table 1 Optimization of reaction conditions.[a]



Entry	Catalyst (mol%)	Yield (%)[b]	*trans*-6a/*cis*-6a[c]
1	$Rh_2(OAc)_4$ (1)	87	50:50
2	$[Ir(cod)Cl]_2$ (1)	83	50:50
3	$[PdCl(\eta^3\text{-}C_3H_5)]_2$(1)	80	50:50
4	$Pd(CH_3CN)_2Cl_2$ (1)	81	50:50
5	CuI (5)	90	50:50
6	$Cu(OTf)_2$ (5)	96	50:50
7	$CuSO_4$ (5)	87	50:50
8	$Cu(CH_3CN)_4PF_6$ (5)	92	50:50
9	$Cu(ClO_4)_2 \cdot xH_2O$ (5)	20	50:50
10	Fe $(ClO_4)_3 \cdot xH_2O$ (5)	<5	-
11[d]	**$Cu(OTf)_2$ (5)**	**98**	**45:55**
12[e]	$Cu(OTf)_2$ (5)	<5	-
13[f]	$Cu(OTf)_2$ (5)	<5	-

[a] Reaction conditions: Unless otherwise noted, the reaction was carried out in a 0.5 mmol scale. To a mixture of glycine ethyl ester hydrochloride (**1a**) and sodium nitrite in 5 mL solvent and 5 mL water, was added H_2SO_4 dropwise at -5 ℃. Then the organic layer was syringed to the mixture of *in situ*-generated isatylidene malononitriles **5a** (0.5 mmol) from **3a** and **4a** at 80 ℃, and $Cu(OTf)_2$ in 5 mL water over one hour via syringe pump at 80 ℃. [b] Isolated yield. [c] *d.r.* ratio was determined by ^1H NMR. [d] EtOAc/H_2O = 1/1 was used as solvent. [e] Pure H_2O was used as solvent. [f] Pure EtOAc was used as solvent.

Next, we seek to make this reaction greener by replacing DCM with more environmentally friendly solvents. Interestingly, ethyl acetate (EtOAc) could give even higher yield than DCM (Table 1, entry 11). According to the GSK's solvent selection guide, EtOAc is considered to be a priority in the chemical process.[9] It should be noted that the reactivity dropped surprisingly when pure EtOAc or pure water is used as the solvent (table 1, entries 12-13), indicating the increased solubility of catalysts and starting material in the mixture of water and EtOAc contributed to the reactivity.

With the establishment of the optimal conditions, we next examined the scope of substrates. Firstly, a variety of isatins were investigated with **1a** as a standard substrate. Isatin derivatives bearing both electron-donating and electron-withdrawing substituents at 5-position gave high to excellent yields of the corresponding products (Table 2, **6b-6g**). The structure of *cis*-**6a** was supported by X-ray crystallography (Table 2, **6a**, CCDC No.: 1899658). For 4, 6, and 7-chloro-substituted isatins, the reaction proceeded smoothly as well, furnishing products in 90-94% yields (Table 2, **6h-6j**). However, when **4a** was replaced by ethyl cyanoacetate (**4b**), the yield of the desired product is unsatisfactory in the copper-catalyzed reaction due to the weaker electrophilicity of isatylidene cyanoacetate compared to **5a**. Reassuringly, when $Cu(OTf)_2$/$Rh_2(OAc)_4$ cocatalyst was applied to the system, the reaction finished smoothly affording **6k** and **6l** with 96% and 60% yields, respectively. The structure of *trans*-**6k** was supported by X-ray crystallography (Table 2, **6k**, CCDC No.: 1941034). The lower yield of **6l** than **6k** may be due to the decrease in electrophilicity of the isatylidene cyanoacetate **5l** which is bearing electron-donating group at 5-position.

Then different diazo esters were explored with **3a** and **4a** as the standard substrates. Under the optimal conditions, *α*-alkyl substituted diazo esters could not be decomposed smoothly by $Cu(OTf)_2$. Gladly, if $Rh_2(OAc)_4$ was used as a cocatalyst, the reaction proceeded smoothly with high efficiency, providing **6** in 78%-83% yields. (Table 3, **6m-6o**). Methyl phenyldiazoacetate showed good reactivity as well, furnishing **6p** in 52% yield. The variance of R^3 group of diazoaceate was allowed, providing products **6q** and **6r** in excellent yields. Notably, the gram-scale reaction was successfully conducted to afford 11 grams of **6q** in 80% yield. Albeit the diastereoselectivities of the products are almost equal to 50:50, these diastereomers could be easily isolated with flash chromatography. For the sake of building compound library for drug discovery, the reaction can facilitate the building up library with stereo-diversity and render a rapid access to the future study on the relationship between stereochemistry and potential functions.

Table 2 Scope of functional isatylidene malononitrile/cyanoacetate in multi-component cascade reactions of **1a**, **3** and **4** in water and EtOAc.[a]

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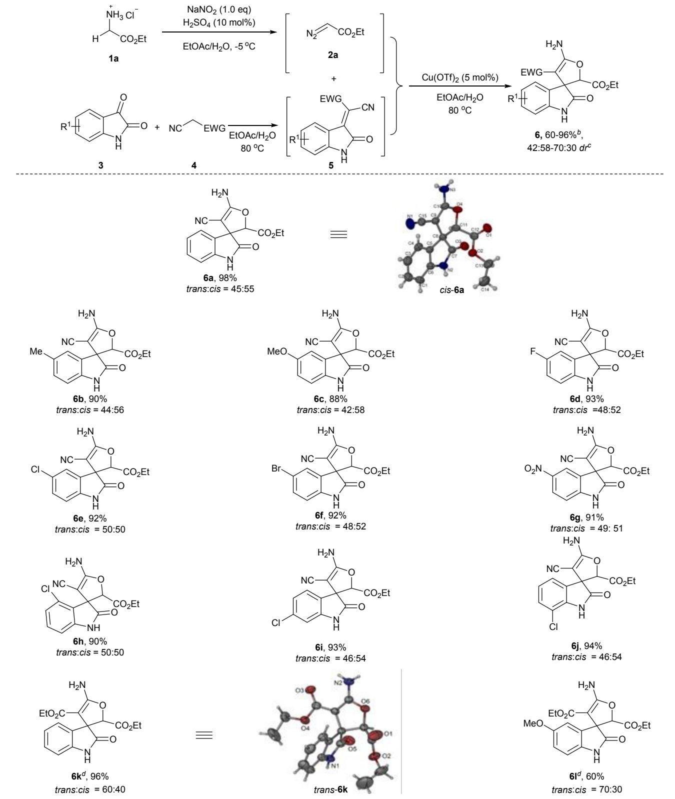
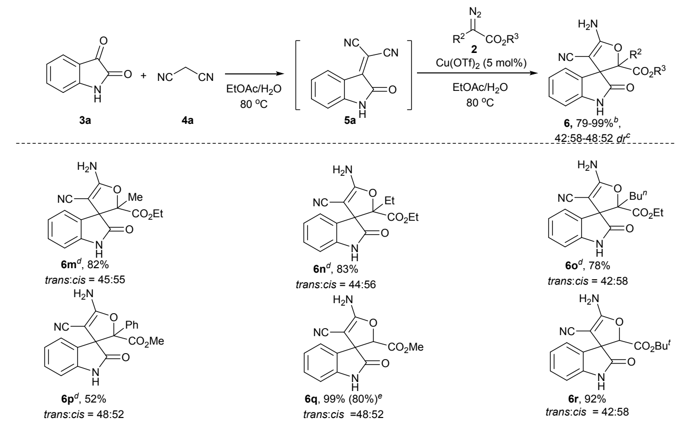


[a] Reaction conditions: Unless otherwise noted, the reaction was carried out in a 0.5 mmol scale. A mixture of glycine ethyl ester hydrochloride (**1a**) and sodium nitrite in 5 mL EtOAc and 5 mL water, was added H_2SO_4 dropwise at -5 ℃. Then the EtOAc layer was syringed to the mixture of *in situ*-generated isatylidene malononitriles **5** (0.5 mmol) from **3** and **4** at 80 ℃, and $Cu(OTf)_2$ in 5 mL water over one hour via syringe pump at 80 ℃. [b] Isolated yield. [c] *d.r.* ratio was determined by ^1H NMR. [d] 1 mol% $Rh_2(OAc)_4$ was used as co-catalyst.

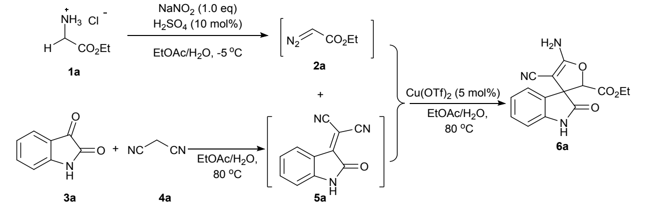
Table 3 Scope of diazo esters in multi-component cascade reactions of **1, 3a** and **4a** in water and EtOAc.[a]



[a] Reaction conditions: Unless otherwise noted, the reaction was carried out in a 0.5 mmol scale. A mixture of diazo ester **2** (2 mmol) in 5 mL EtOAc was syringed to the mixture of *in situ*-generated isatylidene malononitrile **5a** (0.5 mmol) from **3a** and **4a** at 80 ℃, and $Cu(OTf)_2$ in 5 mL water over one hour via syringe pump at 80 ℃. [b] Isolated yield. [c] *d.r.* ratio was determined by ^1H NMR. [d] 1 mol% $Rh_2(OAc)_4$ was used as co-catalyst. [e] Reaction was conducted in gram scale.

Water, acting as a reactant and solvent in the reaction, not only increased the reactivity, but also facilitated the recycling of catalyst $Cu(OTf)_2$. **1a**, **3a** and **4a** were chosen as substrates to conduct the catalyst-recycling experiment. The aqueous phase of catalyst was directly used in the next batch after the simple separation of EtOAc and water. The results remained excellent even after catalyst-recycling for four times (table 4, entries 1-4). However, the yield started to drop to 75% in the 5th batch (table 4, entry 5), and it further reduced to 51% even with longer reaction time (table 4, entry 6). **2a** could not be decomposed in the 7th batch (table 4, entry 7).

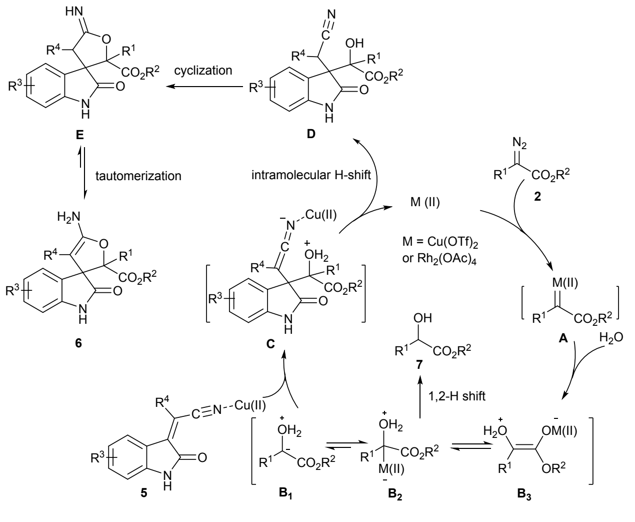
Table 4 Catalyst recycling in multi-component cascade reactions of **1a**, **3a** and **4a** in water and EtOAc.[a]



Batch	Time (min)	Yield (%)[b]	*trans*-6a/*cis*-6a[c]
1	60	98	45:55
2	60	94	45:55
3	60	92	45:55
4	60	92	45:55
5	80	75	45:55
6	120	51	45:55
7	120	0	-

[a] Unless otherwise noted, the reaction was carried out in a 0.5 mmol scale. A mixture of glycine ethyl ester hydrochloride (**1a**) and sodium nitrite in 5 mL EtOAc and 5 mL water, was added H_2SO_4 dropwise at -5 ℃. Then the EtOAc layer was syringed to the mixture of *in situ*-generated isatylidene malononitriles **5a** (0.5 mmol) from **3a** and **4a** at 80 ℃, and $Cu(OTf)_2$ in 5 mL water over one hour via syringe pump at 80 ℃. [b] Isolated yield. [c] *d.r.* ratio was determined by ^1H NMR.

The possible mechanism of the multi-component cascade reaction was elaborated in the Scheme 1. To begin with, carbenoid **A** was generated in the process of the decomposition of *α*-diazo ester **2** catalyzed by $Cu(OTf)_2$ or $Rh_2(OAc)_4$. Then **A** reacted with H_2O to form oxonium ylides, which existed in the form of $\mathbf{B_1}$, $\mathbf{B_2}$ and $\mathbf{B_3}$.[10] If not being trapped by active electrophile, $\mathbf{B_2}$ **was** easily transformed into alcohols **7** via 1,2-H shift. When the electrophile **5** was added, the highly active intermediate **B2** was trapped to produce a Michael-type adduct **C**, which underwent delayed proton transfer to form **D**. Then intermediate **E** was formed via intramolecular nucleophilic addition to the nitrile with hydroxy group. Finally, product **6** were furnished through tautomerization from **E**.



Scheme 1 Proposed mechanism of the multi-component cascade reaction.

Conclusions

In conclusion, a $Cu(OTf)_2$-catalyzed or $Cu(OTf)_2/Rh_2(OAc)_4$-cocatalyzed reaction of *α*-diazo ester, water, isatin and malononitrile/cyanoacetate in one pot was disclosed. This report exhibited a green approach to spiro[2,3-dihydrofuran-3,3′-oxindole] analogues in 60-99% yields. Water plays dual roles in the reaction, acting as a reactant providing hydroxyl source for the final product, and as solvent increasing the reactivity and facilitating the recycling of the catalyst. The catalyst $Cu(OTf)_2$ was reused for 4 times without loss of the yield of **6a**. Notably, the reaction could be scaled up to gram scale by using *in situ* generated methyl diazoacetate and isatylidene malononitrile**,** resulting in 11 g of **6q** after crystallization.

Atom economy, which quantifies the use efficiency of atoms in the staring materials in the chemical process, is a pivotal concept of green chemistry principles. The reactions we reported here have atom economy ranging from 91-93%.[11] And the rest of 7-9% atoms from the starting materials go to the air as the form of innocent nitrogen gas. The application of this method in the synthesis of biologically interesting molecules and identification of bioactivity of the products is ongoing in our lab.

Experimental

General procedure for the synthesis of 6.

To a mixture of glycine ethyl ester hydrochloride (**1a**) and sodium nitrite in 5 mL EtOAc and 5 mL water, was added H_2SO_4 dropwise at -5 ℃. Then the EtOAc layer was syringed to the mixture of in situ-generated isatylidene malononitriles **5** (0.5 mmol) from **3** and **4** at 80 ℃, and $Cu(OTf)_2$ in 5 mL water over one hour via syringe pump at 80 ℃. When the reaction was complete as monitored by TLC, the reaction mixture was separated with a funnel, then the aqueous phase was extracted with ethyl acetate (5 mL×3). The combined organic layers were dried with Na_2SO_4. After filtration, the crude product was purified by flash chromatography on silica gel (petroleum ether: ethyl acetate = 3:1 to 1:1) to provide the corresponding products ***trans*-6** (R_f = 0.25 when PE: EA=1:1) and ***cis*-6** (R_f = 0.2 when PE: EA=1:1).

Procedure for the scale-up synthesis of 6q from glycine methyl ester hydrochloride.

To the 400 mL aqueous solution of **1q** (154 mmol) and sodium nitrite, was added 100 mL EtOAc and 100 mL water. Then 1 M sulfuric acid (1.54 mmol) was added dropwise with funnel at -5 ^oC. The resulting yellow EtOAc solution was washed with $NaHCO_3$ to eliminate the remaining acid. In the other 1000 mL flask, 200 mL EtOAc/H_2O mixture with isatin **3a (**38.60 mmol) was mixed with 200 mL EtOAc/H_2O mixture with malononitrile **4a** at 80 ^oC for 1 h. Then the *in situ*-generated methyl diazoacetate **2q** was added slowly to the solution of isatylidene malononitrile **5a** with 20 mol% $Cu(OTf)_2$ in 400 mL water. After all the methyl diazoacetate added within 2 h, the crude product in organic phase was separated with a funnel and the aqueous phase was extracted with EtOAc (50 mL×3). The combined organic phases were washed with Na_2CO_3, and then brine. Then anhydrous Na_2SO_4 (50 g) was added to the final product solution. After filtration, the solvent was removed to afford solid crude product, which then underwent recrystallization in the mixture of EtOAc and petroleum ether. Eventually, **6q** was obtained (11.4 g, 80% yield) as yellowish white solid.

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Notes and references

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Graphical Abstract

Synthesis of spiro[2,3-dihydrofuran-3,3′-oxindole] via a multi-component cascade reaction of α-diazo esters, water, isatins and malononitrile/ethyl cyanoacetate

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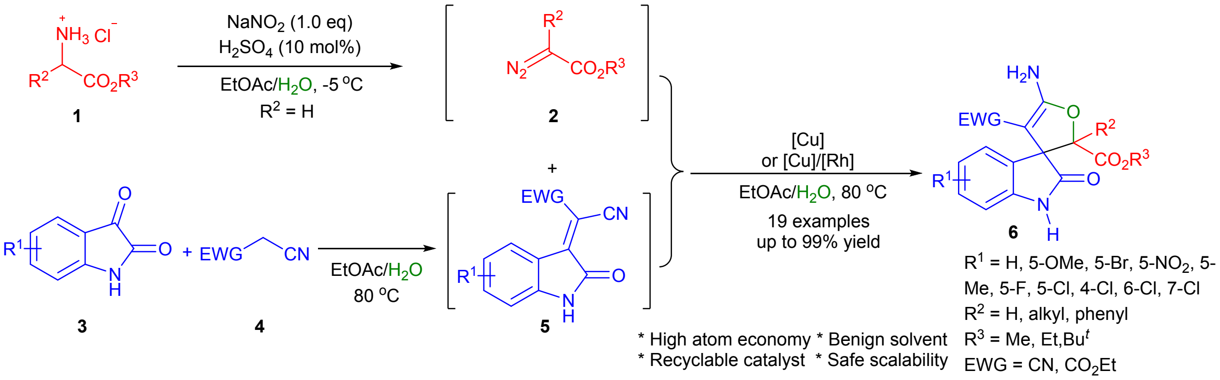

R^1 = H, 5-OMe, 5-Br, 5-NO$_2$, 5-Me, 5-F, 5-Cl, 4-Cl, 6-Cl, 7-Cl
R^2 = H, alkyl, phenyl
R^3 = Me, Et,Bu^t
EWG = CN, CO$_2$Et

* High atom economy * Benign solvent
* Recyclable catalyst * Safe scalability