Dioxygen Activation

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Catalyst-Controlled Highly Selective Coupling and Oxygenation of Olefins: A Direct Approach to Alcohols, Ketones, and Diketones**

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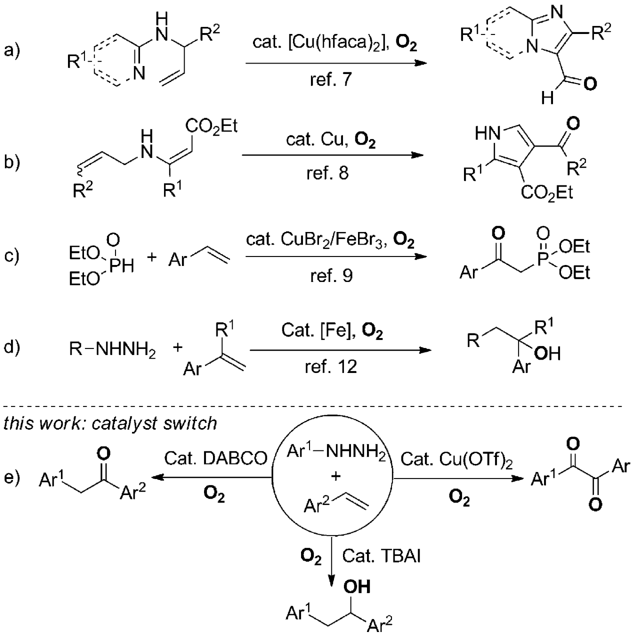
Radical reactions play a very important role in many areas of organic chemistry and polymer chemistry.[1,2] In the past decades, the development of a catalytic system to initiate radical intermediates under mild conditions and to make radical reactions more controllable have been of continuous interest. Among them, transition-metal catalysis has proven to be one of the most highly efficient strategies.[3] Moreover, owing to their low cost, availability, stability, and environmentally friendly nature, copper[4] and iron[5] catalysts have been extensively investigated in radical reactions, and present an attractive prospect for organic synthesis.

Molecular oxygen has been thought of as an ideal oxidant and an atom-efficient reagent in synthetic chemistry.[6] Combining the above two concepts, the Cu- and/or Fe-catalyzed radical addition and oxygenation of alkenes for the synthesis of carbonyl complexes, employing molecular oxygen as the oxygen source, have been significantly developed.[7–9] Zhu and co-workers reported a Cu- catalyzed intramolecular dehydrogenative aminooxygenation started by the addition process of a N-radical intermediate to alkenes (Scheme 1 a).[7] The copper-catalyzed intramolecular relay of a C-radical addition to alkenes that is then captured by molecular oxygen was achieved by the group of Chiba (Scheme 1 b).[8] Ji and co-workers realized a copper and iron cocatalyzed intermolecular oxyphosphorylation of alkenes initiated by a P radical (Scheme 1 c).[9] Furthermore, by using hydrazines as the substrates, which are reported as practical radical precursors,[10] The group of Taniguchi and Ishibashi disclosed an efficient approach to alcohols by the similar radical process (Scheme 1 d).[11,12] Despite the significance of these reactions, this kind of radical oxygenation is still limited, and it remains challenging to control the selectivity from the same starting materials. Herein, we describe a novel catalyst-controlled highly chemoselective coupling and oxygenation of alkenes for the direct synthesis of alcohols, ketones, and diketones (Scheme 1 e), which are important synthons in organic chemistry, important ligands, and biologically active compounds.[13,14]



Scheme 1. Catalyst-controlled oxygenation of alkenes.

Our hypothesis of triggering a tandem radical addition/oxygenation sequence started by investigating the reaction of phenyl hydrazine (**1a**) with styrene (**2a**) (Table 1). Initially, 38 % of **3a** was obtained, along with a trace amount of diketone **4a**, in the absence of any catalyst in acetonitrile (entry 1). When *i*Pr$_2$NEt was used as base, **3a** was obtained in 48 % yield (entry 2). When 1,4-diazabicyclo[2.2.2]octane (DABCO) was used as a base instead of *i*Pr$_2$NEt, the yield of **3a** increased to 55 % (entry 3). Other solvents, such as toluene or dimethylformamide (DMF), were not effective (entries 4 and 5). Significantly, **3a** was isolated in 74 % yield when the loading of anhydrous DABCO was reduced to 40 mol % in the presence of 2.0 equivalents of H$_2$O as an additive (entry 6).

To our delight, a 23 % yield of 1,2-diarylethane-dione (**4a)** was obtained when Cu(OTf)$_2$ was employed as the catalyst (Table 1, entry 7). **4a** was produced in 49 % yield by decreasing the loading of copper(II) catalyst at room temperature (entry 8). The yield of **4a** decreased to 20 %, along with the formation of **3a** (38 %), when the weaker base (NH$_4$)$_2$CO$_3$

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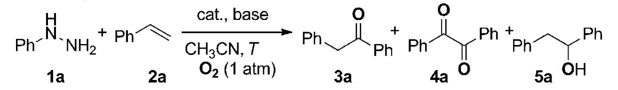
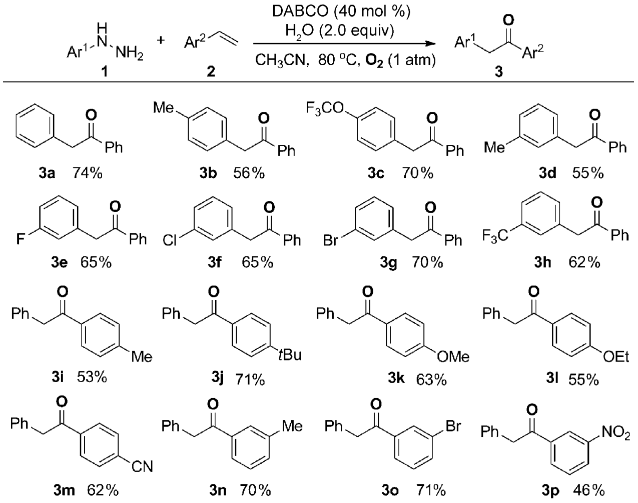
Table 1: Optimization of reaction conditions.[a]

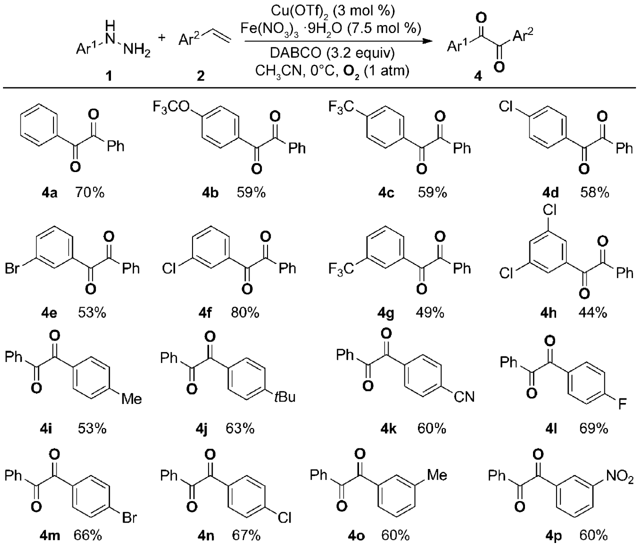


Entry	Cat. (mol %)	Base (equiv)	T [°C]	**3a**[b] [%]	**4a**[b] [%]	**5a**[b] [%]
1	none	none	80	38	trace	0
2	none	*i*Pr_2Net (2.0)	80	48	trace	0
3	none	DABCO (2.0)	80	55	trace	0
4[c]	none	DABCO (2.0)	80	trace	trace	0
5[d]	none	DABCO (2.0)	80	43	trace	0
6[e]	**none**	**DABCO (0.4)**	**80**	**82** **(74)**	**trace**	**0**
7	$Cu(OTf)_2$ (10)	DABCO (0.4)	70	0	23	0
8	$Cu(OTf)_2$ (2)	DABCO (0.4)	25	0	49	0
9	$Cu(OTf)_2$ (2)	$(NH_4)_2CO_3$ (2.0)	25	38	20	0
10	$Cu(OTf)_2$ (2)	none	25	55	0	0
11	$Cu(OTf)_2$ (1) $Fe(NO)_3{\cdot}9H_2O$ (7.5)	DABCO (1.5)	25	0	65 (43)	0
12[f]	$Cu(OTf)_2$ (1) $Fe(NO)_3{\cdot}9H_2O$ (7.5)	DABCO (1.5)	25	0	39	0
13[g]	**$Cu(OTf)_2$ (3)** **$Fe(NO)_3{\cdot}9H_2O$ (7.5)**	**DABCO (3.2)**	**0**	**0**	**72** **(70)**	**0**
14[h]	TBAI (10)	DABCO (1.5)	70	trace	trace	(35)
15[h]	**TBAI (10)**	**pyridine (0.2)**	**70**	**trace**	**trace**	**(41)**
16[h]	I_2 (10)	pyridine (0.2)	70	trace	trace	(25)

[a] Reaction Conditions: **2a** (2.5 mmol), catalyst, base, and additives were added in CH_3CN (4 mL) under O_2 (1 atm), followed by the addition of **1a** (0.5 mmol). [b] Yields determined by GC analysis; yields of isolated products are shown in parentheses. [c] The reaction was carried out in toluene. [d] The reaction was carried out in DMF. [e] H_2O (2.0 equiv) was added. [f] TBAB (0.1 equiv) was added. [g] 4-methoxyaniline (2.0 equiv) was added. [h] **2a** (0.5 mmol), **1a** (1.0 mmol). A mixture of CH_3CN (0.5 mL) and H_2O (1.5 mL) was used as the solvent.



Scheme 2. Transition-metal-free selective synthesis of 1,2-diarylethanone. For reaction Conditions, see Table 1, entry 6. Yields shown are of isolated products.



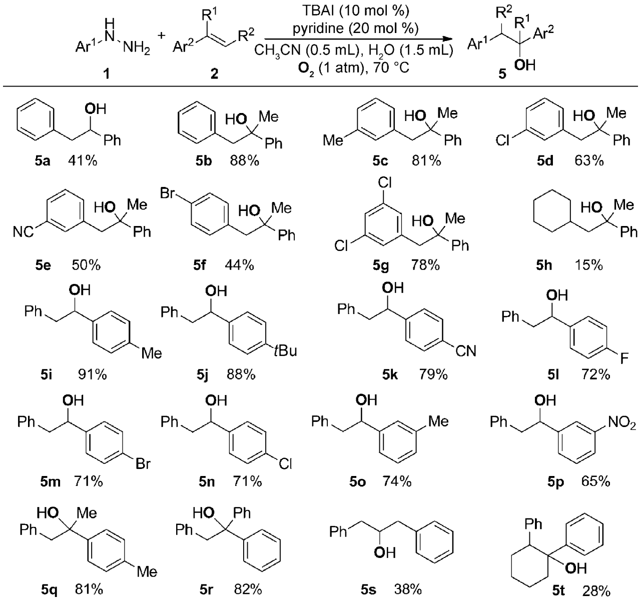
Scheme 3. Cu- and Fe-cocatalyzed selective synthesis of 1,2-diarylethane-dione. For reaction Conditions, see Table 1, entry 13. Yields shown are of isolated products.

was employed (entry 9). In the absence of a base, **4a** was not detected, but rather **3a** was obtained in 55 % yield (entry 10). Gratifyingly, the expected diketone product **4a** was isolated in 70 % yield when $Cu(OTf)_2$ (3 mol %) and $Fe(NO_3)_3{\cdot}9H_2O$ (7.5 mol %) were used as cocatalysts[15] at 0 °C (entry 13). The use of tetrabutylammonium bromide (TBAB; 10 mol %) as a phase transfer catalyst did not improve the efficiency of this transformation (entry 12).

The alcohol product **5a** was selectively obtained in 35 % yield when the reaction was carried out in the presence of catalytic amount of tetrabutylammonium iodide (TBAI; entry 14, Table 1). After screening different parameters, the standard conditions for the selective alcohol synthesis were determined to be: TBAI (10 mol %), pyridine (20 mol %), a mixture of CH_3CN (0.5 mL) and H_2O (1.5 mL) as solvent, O_2 (1.0 atm), 70 °C, under which, alcohol **5a** was obtained in 41 % yield (entry 15).

With the optimal reaction conditions in hand, we subsequently investigated the substrate scope of this highly selective method (Schemes 2, 3 and 4). The transition-metal-free aerobic oxidative coupling of aryl hydrazines and substituted styrenes is summarized in Scheme 2. Not only electron-rich groups, such as *p*-methyl (**3b**) and *m*-methyl (**3d**), but also electron-deficient groups, such as *m*-CF_3 (**3h**) on the aryl ring of the aryl hydrazines could drive the reaction smoothly in moderate yield. Halo-substituted aryl hydrazines also performed well under the standard conditions, generating the halo-substituted products. Moreover, this transformation proceeded smoothly and in moderate yields with electron-rich styrenes that contain electron-donating groups, such as *p*-methyl (**3i**), *p*-*tert*-butyl (**3j**), *p*-methoxy (**3k**), *p*-ethoxy (**3l**) and *m*-methyl (**3n**), on the aryl ring. Substituted styrenes with electron-withdrawing groups are also tolerated in this transformation (**3m**, **3o**, and **3p**).

Furthermore, under copper and iron cocatalyzed conditions, various 1,2-diarylethane-diones were obtained in moderate yields from corresponding aryl hydrazines and substituted styrenes (Scheme 3). Aryl hydrazines bearing electron-withdrawing groups such as CF_3 (**4c** and **4g**) performed well, giving yields of 59 % and 49 %, respectively. Halo-substituted



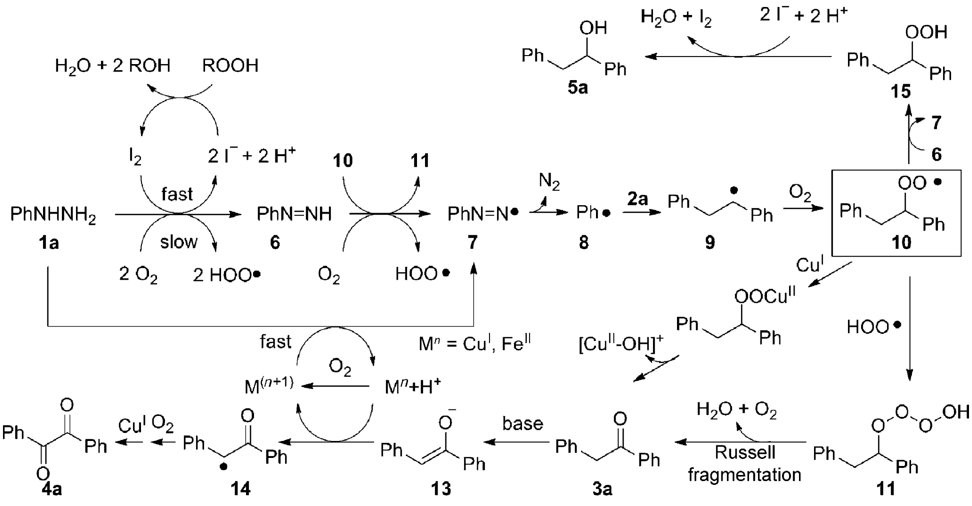
Scheme 4. TBAI catalyzed selective synthesis of alcohols. For reaction Conditions, see Table 1, entry 15. Yields shown are of isolated products.

products **4d**, **4e**, **4f**, and **4h** were also obtained in moderate to good yield. Styrenes bearing electron-withdrawing and electron-donating substituents at the aryl ring can be efficiently transformed into the corresponding diketone products.

When using TBAI, various 1,2-diarylethanols were obtained in moderate to good yields from the corresponding aryl hydrazines and substituted styrenes (Scheme 4). The reaction with cyclohexylhydrazine also works under these conditions, but with low yield (**5h**). Furthermore, allylbenzene and multi-substituted styrene were tolerated in this transformation, forming the corresponding alcohols (**5s** and **5t**)[16] in 38% and 28% yield, respectively. Therefore, substituted alcohols, ketones, and diketones can be prepared by this this aerobic coupling and oxygenation strategy in a highly chemoselective manner from the same simple olefins by selecting a different catalyst.

To further understand these transformations, control experiments with $^{18}O_2$ and $H_2{}^{18}O$ isotopic labeling were investigated. It was found that the oxygen of the newly formed carbonyl group of 1,2-diarylethanone **3a** was wholly from oxygen molecular, rather than from H_2O (Supporting Information, Eqs. (S1) and (S2); determined by HRMS). On the other hand, [^{18}O]**4a** and [^{18}O]**5b** were obtained when $^{18}O_2$ (1 atm) and $H_2{}^{16}O$ were used (Eqs. (S3) and (S5); determined by HRMS). Reaction in the presence of $H_2{}^{18}O$ under $^{16}O_2$ (1 atm) afford **4a** and **5b** without the formation of [^{18}O]**4a** and [^{18}O]**5b** (Eqs. (S4) and (S6); determined by HRMS). These isotopic labeling results clearly demonstrate that the oxygen atoms of **3a**, **4a**, and **5b** originated from O_2. Furthermore, when the reaction mixture was analyzed by GCMS, we found that **1a** was converted into **3a** after 15 min. After 16 h, **4a** was completely produced from **3a**. This result indicated that the formation of **4a** is a relay process with **3a** as the intermediate.

On the basis of the above results and previous work, a proposed mechanism for the selective coupling and oxygenation of alkenes and hydrazines is shown in Scheme 5. As previously reported,[10a] phenyl radical **8** and a large amount of hydroperoxyl radical (HOO·) are initially generated from **1a** and oxygen with the release of N_2 in the presence of base. These transformations go faster when high-oxidation-value transition-metal salts (Cu^{II} and Fe^{III})[11,12,17] or iodine[18] are used as oxidants. The key intermediate **10** is provided by the formation of **9** and its subsequent addition to oxygen.[17a] In a transition-metal- and iodine-free system, the benzyl peroxy radical **10** couples with the hydroperoxide radical (HOO·) to form a monoalkyl tetroxide **11**, which decomposes to afford the desired product **3a**, along with the formation of molecular oxygen and water through Russell fragmentation.[19] On the other hand, because of the low concentration of hydroperoxide radical in the Cu- and Fe- cocatalytic system,[20] **3a** is generated through intermediate **12** followed by elimination of CuOH.[21] Furthermore, intermediate **13**, which is generated from **3a**, could be continuously oxidized by Cu- and/or Fe-salts and molecular oxygen to form benzyl radical **14**, which can undergo the same oxidative processes again (as benzyl radical **9**) to form the second carbonyl group of diketone product **4a**. In the TBAI catalytic pathway, with a low concentration of hydroperoxide radical, intermediate **10** abstracts a H atom from the strong H-donor **6** to provide hydroperoxide **15**, along with the formation of radical intermediate **7** to complete the chain propagation step. Subsequently, the hydroxylation product **5a** is afforded by



Scheme 5. Proposed mechanism.

hydroperoxide **15** through Landolt reaction with the regeneration of iodine.[22,23] The by-products benzene,[10a] bibenzyl, and stilbene[24] were detected by GCMS, which indicated that intermediates **8** and **9** are involved in this transformation.

In summary, we have developed a novel catalyst-controlled highly chemoselective coupling and oxygenation of olefins for the direct synthesis of substituted alcohols, ketones, and diketones. Molecular oxygen not only participates as an oxidant, but also undergoes dioxygen activation through a radical process. The selectivity for the synthesis of substituted alcohols, ketones, and diketones, which are important synthons, important ligands, and biologically active compounds, is readily switched by the selection of different catalysts. Further studies on the mechanism and synthetic application of these reactions are ongoing in our group.

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