Radical Cascades

Deutsche Ausgabe: DOI: 10.1002/ange.201411974
Internationale Ausgabe: DOI: 10.1002/anie.201411974

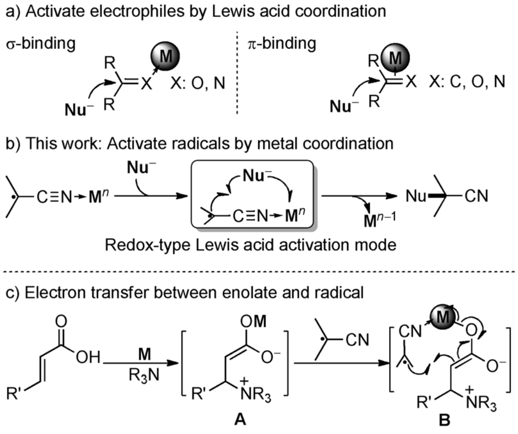
Metal Bridging for Directing and Accelerating Electron Transfer as Exemplified by Harnessing the Reactivity of AIBN**

*Yinjun Xie, Shengmei Guo, Longmin Wu, Chungu Xia, and Hanmin Huang**

Abstract: *A new strategy for tuning the electron transfer between radicals and enolates has been developed. This method elicits the innate reactivity of AIBN with a copper catalyst and enables a cascade reaction with cinnamic acids. Electron paramagnetic resonance studies and control experiments indicate that the redox-active copper species not only activates the radical by coordination, but also serves as a bridge to bring the radical and nucleophile within close proximity to facilitate electron transfer. By exploiting possible combinations of redox-active metals and radical entities with suitable coordinating functional groups, this strategy should contribute to the development of a broad range of radical-based reactions.*

Electron transfer between molecules is a fundamental process of many important transformations in biology and chemistry that plays a vital role in controlling the reactivity and selectivity of a reaction.[1] As a result, the design of efficient catalysts and the discovery of effective activation modes to direct and accelerate the electron transfer between molecules are two important issues in catalysis. In this context, a successful and intensively studied approach to promote electron transfer is based on the use of transition metals to bridge reactants through coordination.[2] Upon coordination, the LUMO of an electrophile is reduced in energy, and the resulting assembly provides a suitable environment for facilitating electron transfer (Scheme 1 a). Whereas such a strategy is commonly employed for polar reactions, its use for harnessing the reactivity of free radicals remains, to the best of our knowledge, largely unexplored, despite the significant advances in radical chemistry over the last few decades.[3]

Free radicals have long been recognized as highly reactive species in many transformations; however, challenges related to selectively controlling their reactivity are often encountered.[4] More and more radical reactions that involve transition metals have been developed. Generally, the role of the transition metal is limited to the generation of free radicals or the transformation of radicals into their ionic counterparts, rather than activating them for directing the bond formation.[5] However, once a suitable coordinating functional group has been introduced in a free radical, it should be possible to activate the radical for directing bond formation by coordination to a metal. AIBN [azobis(isobutyronitrile)] is one of the most widely used radical initiators in polymer chemistry and radical-mediated organic synthesis. It usually does not get involved as a reactant in either radical or polar reactions, although AIBN might be used as a cyanide source in organic synthesis. This is in part due to the inherently low nucleophilicity and electrophilicity of the isobutyronitrile radical derived from AIBN.[6] Inspired by the fact that the nitrile group is a known ligand for various metals, we envisioned that the isobutyronitrile radical would be activated by coordination to a metal, and that the electron transfer between the radical and a nucleophile would consequently be accelerated (Scheme 1 b).[7a]



Scheme 1. New strategy for the activation of free radicals.

The successful implementation of this strategy calls for the identification of a redox-active metal catalyst that not only coordinates to the isobutyronitrile radical, but is also prone to accepting one electron from a nucleophile. It is also essential to carefully select a suitable nucleophile that could bind to the metal center to ensure that a single electron transfer (SET) process occurs. Copper salts, which have not only been shown to be robust redox-active catalysts for both two-electron and single-electron processes, but also good Lewis acids for nitrile coordination, were selected as possible catalysts.[8] Zwitterionic enolates generated in a Morita–Baylis–Hillman (MBH) reaction[9] were chosen as the nucleophiles for testing our hypothesis for the following reasons: 1) Enolates can act as electron donors to participate in metal-mediated SET reactions,[10] and 2) functional groups contained in the zwitterionic enolates could provide useful binding sites to coordinate

---

[*] Dr. Y. Xie, Dr. S. Guo, Prof. L. Wu, Prof. C. Xia, Prof. Dr. H. Huang
State Key Laboratory for Oxo Synthesis and Selective Oxidation
Lanzhou Institute of Chemical Physics
Chinese Academy of Sciences
Lanzhou 730000 (China)
E-mail: hmhuang@licp.cas.cn

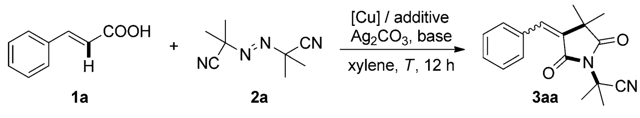
[**] This research was supported by the Chinese Academy of Sciences, the National Natural Science Foundation of China (21222203, 21372231, and 21133011). We thank Prof. Yu Lan of Chongqing University for theoretical calculations and helpful discussions. AIBN = azobis(isobutyronitrile).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201411974.

a metal. We thus selected cinnamic acids (**1**) as suitable substrates because of their electron-deficient nature and the possibility of the carboxylate moiety acting as a ligand for copper (Scheme 1c). It was expected that exposure of **1** to a suitable tertiary amine in the presence of a copper salt would furnish a zwitterionic enolate **A**, which might capture the isobutyronitrile radical to form complex **B**. The coordination of the radical, which results in a lower-energy SOMO, together with the well-organized aggregation would facilitate the SET between radical and enolate. Herein, we report a new strategy to direct and accelerate the electron transfer between free radicals and enolates, which enabled the development of a new cascade reaction between AIBN and α,β-unsaturated acids. This method provides a rapid approach for the synthesis of functionalized pyrrolidine-2,5-diones, which are important moieties in a wide range of biologically active molecules.[11]

To put our design into practice, the reaction of cinnamic acid (**1a**) and AIBN (**2a**) was first studied in the presence of a catalytic amount of $CuBr_2$ and a stoichiometric amount of Et_3N and Ag_2CO_3 (Table 1, entry 1). To our delight, heterocycle **3aa**, with a pyrrolidine-2,5-dione moiety, was obtained in 37% yield when the reaction was conducted at 120°C in xylene. The structure of **3aa** was determined by single-crystal X-ray diffraction analysis.[12] The product **3aa** could be viewed as the addition of two isobutyronitrile radicals to the cinnamic acid skeleton. Afterwards, we started to optimize the reaction conditions by screening different copper catalysts. As shown in Table 1, both Cu^I and Cu^{II} salts can catalyze this transformation, and CuBr was found to be the most efficient, affording product **3aa** in 44% yield (entries 1–6). With CuBr as the catalyst, other reaction parameters were screened to maximize the efficiency of this cascade reaction. The use of 1,4-diazabicyclo[2.2.2]octane (DABCO) as the amine and Ag_2CO_3 as the oxidant gave the desired heterocycle in 59% yield after heating at 100°C for twelve hours (see the Supporting Information). As alcohols and H_2O have been shown to be beneficial for stabilizing the zwitterionic intermediates in MBH reactions,[13] we screened several alcohols as additives and found that 2-amino-3-phenylpropan-1-ol (PPA) with H_2O was optimal. Under these conditions, compound **3aa** was isolated in 74% yield with the thermodynamically more stable *Z* isomer as the major product (*E*/*Z* = 30:70; entry 14). Further control experiments confirmed that the substrates were unreactive in the absence of either copper salts or tertiary amines, indicating the importance of the tertiary amine for generating the zwitterionic enolate and of the copper catalysts for accelerating the electron transfer (entries 15 and 16). Moreover, when some typical MBH substrates, such as methyl cinnamate, chalcone, and phenylbut-3-en-2-one,[9] were subjected to the optimized reaction conditions, these α,β-unsaturated carbonyl compounds were completely recovered (see the Supporting Information). These observations strongly suggest that the COOH moiety of **1a** is a prerequisite for this reaction.

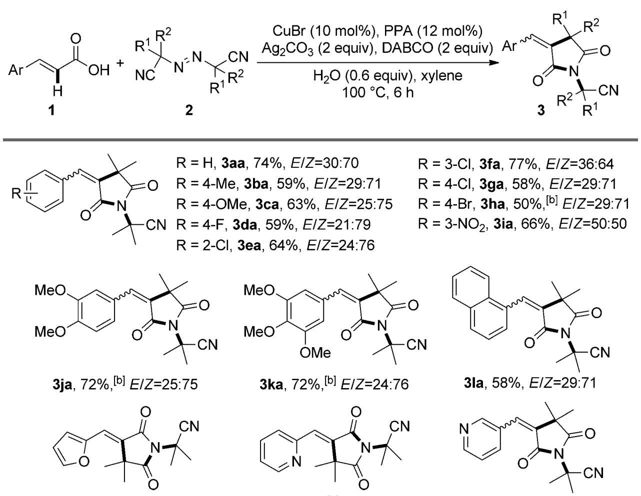
Table 1: Optimization of the reaction conditions.[a]



Entry	[Cu]	Base	Additive	*T* [°C]	Yield [%]
1	$CuBr_2$	Et_3N	–	120	37
2	CuBr	Et_3N	–	120	44
3	$CuCl_2$	Et_3N	–	120	42
4	CuI	Et_3N	–	120	11
5	$Cu(OTf)_2$	Et_3N	–	120	24
6	$[Cu(acac)_2]$	Et_3N	–	120	21
7	CuBr	DABCO	–	120	59
8	CuBr	DABCO	–	100	59
9	CuBr	DABCO	–	80	51
10[b]	CuBr	DABCO	–	100	60
11[b]	CuBr	DABCO	PPh_3	100	59
12[b,c]	CuBr	DABCO	EG	100	63
13[b,d]	CuBr	DABCO	EG/H_2O	100	70[f]
14[b,e]	CuBr	DABCO	PPA/H_2O	100	74[f]
15[b]	–	DABCO	–	100	0
16[b]	CuBr	–	–	100	0

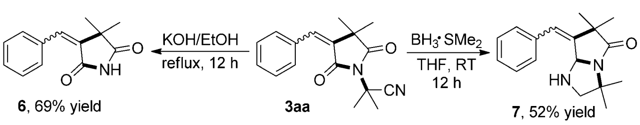
[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), [Cu] (0.05 mmol, 10 mol%), base (1.0 mmol), Ag_2CO_3 (1.0 mmol), and xylene (2 mL) at 120°C for 12 h. Yields were determined by GC analysis. *E*/*Z* ratios in the range of 46:54 to 30:70. [b] 6 h. [c] EG (0.06 mmol). [d] EG (0.06 mmol), H_2O (0.3 mmol). [e] PPA (0.06 mmol), H_2O (0.3 mmol). [f] Yield of isolated product.

Table 2: Substrate scope.[a]

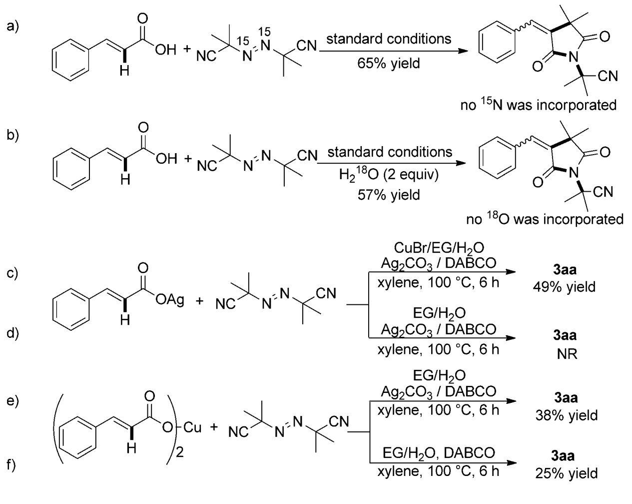


[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), CuBr (0.05 mmol, 10 mol%), Ag_2CO_3 (1.0 mmol), DABCO (1.0 mmol), PPA (0.06 mmol, 12 mol%), H_2O (0.3 mmol), and xylene (2 mL) at 100°C for 6 h. Yields of isolated products are given; the *E*/*Z* ratios were determined by GC analysis before isolation. [b] EG (0.06 mmol, 12 mol%) was used instead of PPA. [c] 10 h.

With the optimized conditions established, the generality of this transformation was investigated. A series of cinnamic acids with electron-donating or -withdrawing groups gave the desired products **3aa**–**3ka** in good yields (Table 2). The steric hindrance of the substituents on the aryl ring of the cinnamic acids did not exert a strong influence on the reactivity (**3ja** vs. **3ka**). Aside from the cinnamic acids, naphthyl-substituted acrylic acid **1l** was also effectively transformed into the corresponding adduct **3la** in 58% yield. Furthermore, the method was proven to be equally effective for heteroaryl-substituted acrylic acids (**3ma**, **3na**, **3oa**, and **3pa**). Notably, when the *E*-configured substrates **1m** and **1n** were used, only the *E* isomers of the corresponding products were obtained (**3ma** and **3na**).[12] The high stereoselectivity for the *E* isomer can be attributed to the heteroatoms in the *ortho* position of the aromatic ring, which coordinate to the copper center during the catalytic process. Finally, other nitrile-containing radicals, derived from 2,2′-azobis(2-methylbutyronitrile) (AMBN) and 1,1′-azobis(cyclohexane-1-carbonitrile) (ACCN), also reacted with cinnamic acid (**1a**) to afford the corresponding products **3ab** and **3ac** in 51% and 36% yield, respectively. The product **3aa** could be converted into pyrrolidine-2,5-dione **6** by cleavage of the C–N bond upon exposure to KOH. Furthermore, **3aa** could also be used as the starting material for construction of the N-fused bicyclic compound **7** in a one-step functional group transformation.



To get insights into the mechanism of this transformation, several control experiments were conducted (Scheme 2). Initially, when ^{15}N-labeled AIBN (the azo nitrogen atoms were labelled with ^{15}N) was treated with **1a** under the standard conditions, the resulting product was analyzed by high-resolution mass spectrometry, which showed that the ^{15}N atoms of the azo moiety had not been incorporated into the product. This result confirmed that the N atoms of the product originated from the nitrile groups of AIBN. Moreover, the addition of two equivalents of $H_2{}^{18}O$ showed that the amide was not formed by hydrolysis with H_2O and that the O atom of the product originated from cinnamic acid, as no ^{18}O-containing product was detected. Furthermore, when a radical scavenger, such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO), was added, the reaction was almost completely suppressed (see the Supporting Information). These results demonstrated that a radical process was involved in this reaction.



Scheme 2. Control experiments.

After confirming the origin of the N and O atoms in the product, we further explored the roles of the copper and silver salts. As cinnamic acid could react with CuBr and Ag_2CO_3 to form the corresponding salts, the silver and copper cinnamate salts were prepared separately and subjected to this reaction. When cinnamic acid was replaced by cinnamoyloxysilver, the reaction did not take place in the absence of a catalytic amount of CuBr, revealing that the copper catalyst was essential for this reaction (Scheme 2c,d). Meanwhile, when bis(cinnamoyloxy)copper was used as the substrate instead of cinnamic acid, product **3aa** was obtained regardless of the presence of a stoichiometric amount of Ag_2CO_3 (Scheme 2e,f). These observations indicate the essential role of copper as a catalyst and that Ag_2CO_3 probably acts as an oxidant to re-oxidize the Cu^I to a Cu^{II} species to close the catalytic cycle.

To get further insights into how the copper bridging directs and accelerates the electron transfer in this reaction, we investigated the interaction of the Cu^{II} species with the reactants by electron paramagnetic resonance (EPR) spectroscopy.[14] As shown in Figure 1, initially, when a catalytic amount of $CuBr_2$ was treated with **1a** (10 equiv) in DMSO at 100 °C for two hours, the resulting solution exhibited a typical axial Cu^{II} EPR signal (line 2), identical to that of a DMSO solution of $CuBr_2$ (line 1). Moreover, the strong EPR signal of Cu^{II} with a lower g value was further observed when a catalytic amount of $CuBr_2$ was treated with **1a** (10 equiv) and DABCO (20 equiv) in DMSO at 100 °C for two hours. These data excluded the possibility that cinnamic acid **1a** was transformed into an electrophilic radical species by oxidation with $CuBr_2$ as no electron transfer occurred between the Cu^{II} species and cinnamic acid. Furthermore, a typical axial Cu^{II} EPR signal was also detected when $CuBr_2$ was treated with AIBN (20 equiv) in DMSO at 100 °C for two hours. This result indicated that SET did not take place between $CuBr_2$ and the isobutyronitrile radical, ruling out the involvement of an isobutyronitrile ion in the present reaction. Furthermore, essentially the same Cu^{II} EPR signal was observed when $CuBr_2$ was exposed to AIBN (20 equiv) and cinnamic acid **1a** (10 equiv) in DMSO (100 °C, 2 h), indicating that SET could not occur in the absence of DABCO. We expected that once DABCO had been introduced to the above system, the zwitterionic enolate would form, and the SET process should proceed rapidly. Indeed, when a catalytic amount of $CuBr_2$ was treated with **1a** (10 equiv), AIBN (20 equiv), and DABCO (20 equiv) in DMSO at 100 °C, the Cu^{II} EPR signal quickly disappeared within ten minutes (Figure 1b), and the desired cyclization product **3aa** was detected by GC-MS. Analysis of the copper residue by X-ray photoelectron spectroscopy (XPS) indicated that a Cu^I species had been formed (see the Supporting Information). These data excluded the participation of isobutyronitrile ion and enolate radical intermediates in this reaction and corroborated our

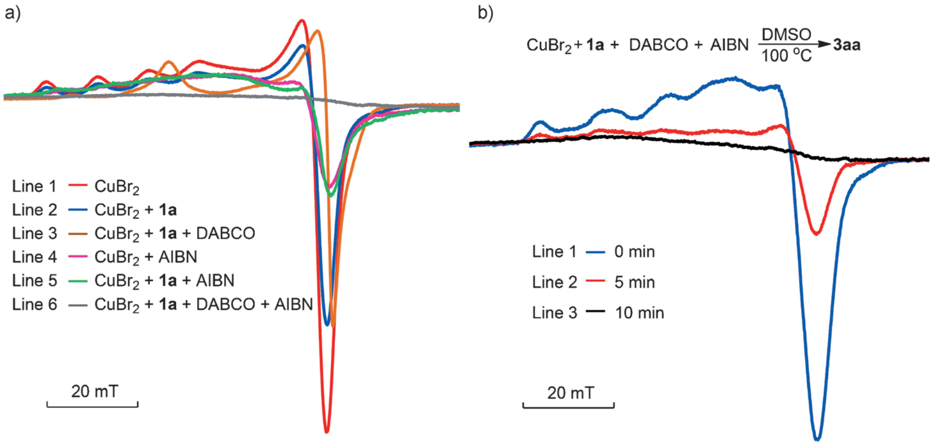


Figure 1. a) EPR spectra of $CuBr_2$ treated with different reactants; measured at 200 K. b) Evolution of the EPR spectra of the standard reaction mixture with time; measured at 200 K.

hypothesis that SET took place between the isobutyronitrile radical and the zwitterionic enolate derived from cinnamic acid. Therefore, activation mode **B** (Scheme 1 c) most likely constitutes the approach of the isobutyronitrile radical to the zwitterionic enolate in this cascade reaction.

On the basis of the control experiments and EPR studies, a reaction mechanism was proposed (Figure 2). Initially, exposure of **1a** to the copper salt in the presence of DABCO and the silver salt leads to the generation of zwitterionic enolate **A**, which captures the free isobutyronitrile radical (generated from AIBN) to form intermediate **B**. The coordination of the nitrile group to the Cu^{II} species renders the radical species more electrophilic, and the resulting Cu bridge brings the radical and the enolate closer together, facilitating the SET between radical and enolate through intermediate **C** with the construction of a new C–C bond.[7] Subsequently, a retro-aza-Michael addition takes place to eliminate the DABCO cation and generate intermediate **D**. For (*E*)-3-(thiophen-2-yl)acrylic acid and (*E*)-3-(pyridin-2-yl)acrylic acid, which feature heteroatoms at neighboring positions, the chelated intermediate **C′** might be involved, leading to the exclusive formation of the *E* isomer. Oxidation of the Cu^{I} to the Cu^{II} species by Ag^{I} increases its Lewis acidity and enables the coordinated nitrile to be attacked by an oxygen anion to afford Cu–N species **E**. The active Cu^{II} species **E** captures another isobutyronitrile radical by coordination via its nitrile group to form intermediate **F**. Subsequent SET breaks the Cu–N bond and forms a C–N bond, releasing a Cu^{I} species and intermediate **G**. Finally, rearrangement[15] of **G** leads to product **3aa**.

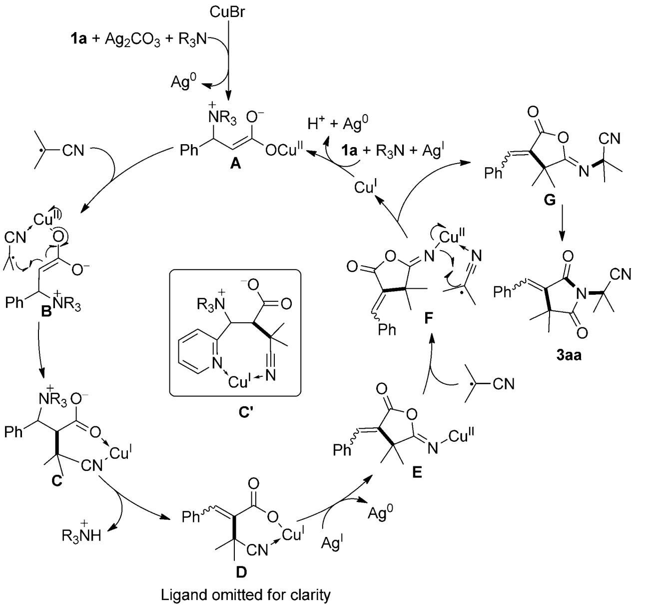
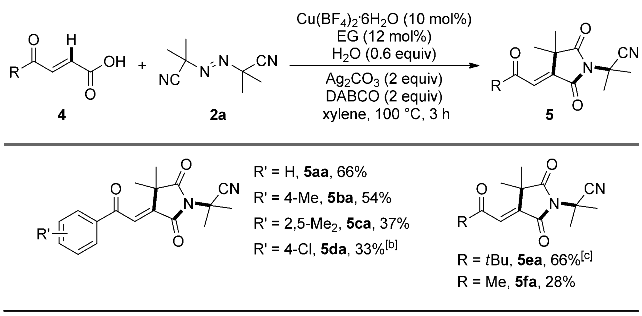


Figure 2. Plausible reaction mechanism.

Several additional experiments and analyses provided further evidence for this mechanism. A cross-over experiment with **1a**, AIBN (**2a**), and AMBN (**2b**) as the reactants was carried out under the standard conditions, and the products **3aa** and **3ab** were obtained together with the cross-over products in a ratio of approximately 1:1:1. This result confirmed that the delivery of the second radical to intermediate **F** occurred in an intermolecular fashion (see the Supporting Information).[16] Trace amounts of 2,2-dimethyl-4-phenylbut-3-enenitrile and 4-benzylidene-3,3-dimethylpyrrolidine-2,5-dione were detected in the standard reaction, suggesting the plausible intermediacy of **D** in the catalytic cycle. Moreover, when 4-benzylidene-3,3-dimethylpyrrolidine-2,5-dione was treated with AIBN under the standard conditions, the desired product **3aa** was not detected, indicating the necessity of the intermediacy of **E** or **F** in the catalytic cycle. Computational studies revealed that the SOMO energy of the isobutyronitrile radical was indeed reduced by 1.59 eV when the radical was coordinated to a copper species (see the Supporting Information), which is consistent with our initial hypothesis.

Finally, to explore this method in more complex settings, substrates with two carbonyl groups were synthesized and investigated under the reaction conditions. As such, (*E*)-4-oxo-4-phenylbut-2-enoic acid (**4a**) was identified as a desirable substrate for testing the practicability of our strategy. Using the procedure in Table 3, the cascade reaction with AIBN afforded cyclization product **5aa** in 66% yield. As expected, the keto carbonyl group remained intact, and the reaction took place exclusively at the carboxyl group, affording the *E* isomer as the sole product.[12] Similar results were obtained with aryl- and alkyl-substituted unsaturated keto-acids. The desired reactions proceeded smoothly to give the corresponding products in moderate to good yields with completely *E* selectivity under the current reaction conditions.

Table 3: Unsaturated ketoacids as substrates.[a]



[a] Reaction conditions: **4** (0.5 mmol), **2** (1.0 mmol), $Cu(BF_4)_2 \cdot H_2O$ (0.05 mmol, 10 mol%), Ag_2CO_3 (1.0 mmol), DABCO (1.0 mmol), EG (0.06 mmol, 12 mol%), H_2O (0.3 mmol), and xylene (4 mL) at 100 °C for 3 h. Yields of isolated products are given. [b] 120 °C. [c] 90 °C.

In summary, we have developed a conceptually new strategy for directing and accelerating the single electron transfer between free radicals and enolates by bridging the two reactants with a metal species. A redox-active copper species was used for the activation of the free radical and for bringing the radical and enolate closer together to facilitate electron transfer. We demonstrated the remarkable ability of this strategy for harnessing the reactivity of the isobutyronitrile radical, which is generally not considered as a structural contributor. This approach enabled the development of a cascade reaction for the synthesis of highly functionalized pyrrolidine-2,5-diones from readily available cinnamic acids and AIBN. We believe that these results may inspire future research efforts towards the development of transition-metal-catalyzed radical reactions, especially those featuring radical species as electrophilic intermediates.

Keywords: AIBN · cinnamic acids · copper · enolates · single-electron transfer

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 5900–5904
Angew. Chem. **2015**, *127*, 5998–6002

---

[1] For selected reviews on electron transfer, see: a) L. Eberson, *Adv. Phys. Org. Chem.* **1982**, *18*, 79; b) A. Pross, *Acc. Chem. Res.* **1985**, *18*, 212; c) J. K. Kochi, *Acc. Chem. Res.* **1992**, *25*, 39; d) A. Houmam, *Chem. Rev.* **2008**, *108*, 2180; e) B. M. Rosen, V. Percec, *Chem. Rev.* **2009**, *109*, 5069; f) A. Kumar, M. D. Sevilla, *Chem. Rev.* **2010**, *110*, 7002; g) J. L. Dempsey, J. R. Winkler, H. B. Gray, *Chem. Rev.* **2010**, *110*, 7024; h) C. M. Paquete, R. O. Louro, *Acc. Chem. Res.* **2014**, *47*, 56; i) R. Pérez-Ruiz, M. C. Jiménez, M. A. Miranda, *Acc. Chem. Res.* **2014**, *47*, 1359; j) J. Broggi, T. Terme, P. Vanelle, *Angew. Chem. Int. Ed.* **2014**, *53*, 384; *Angew. Chem.* **2014**, *126*, 392.

[2] a) *Lewis acids and selectivity in organic synthesis* (Eds.: J. M. Pons, M. Santelli), CRC, Boca Raton, **1996**; b) *Lewis acids in organic synthesis* (Ed.: Y. Yamamoto), Wiley-VCH, Weinheim, **2000**; c) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209; d) Y. Yamamoto, *J. Org. Chem.* **2007**, *72*, 7817.

[3] a) *Radicals in Organic Synthesis* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Boca Raton, **2001**; b) A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* **2011**, *50*, 5018; *Angew. Chem.* **2011**, *123*, 5122; c) A. Studer, D. P. Curran, *Nat. Chem.* **2014**, *6*, 765.

[4] B. Quiclet-Sire, S. Z. Zard, *Pure Appl. Chem.* **1997**, *69*, 645.

[5] For reviews, see: a) J. Iqbal, B. Bhatia, N. K. Nayyar, *Chem. Rev.* **1994**, *94*, 519; b) L. Ford, U. Jahn, *Angew. Chem. Int. Ed.* **2009**, *48*, 6386; *Angew. Chem.* **2009**, *121*, 6504; c) U. Jahn, *Top. Curr. Chem.* **2012**, *320*, 121; d) U. Jahn, *Top. Curr. Chem.* **2012**, *320*, 191; e) U. Jahn, *Top. Curr. Chem.* **2012**, *320*, 323; f) Q. Liu, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 13871; *Angew. Chem.* **2013**, *125*, 14115; g) L. J. Sebren, J. J. Devery III, C. R. J. Stephenson, *ACS Catal.* **2014**, *4*, 703; h) S. Sumino, A. Fusano, T. Fukuyama, I. Ryu, *Acc. Chem. Res.* **2014**, *47*, 1563.

[6] F. De Vleeschouwer, V. Van Speybroeck, M. Warroquier, P. Geerlings, F. De Proft, *Org. Lett.* **2007**, *9*, 2721.

[7] a) M. H. Dickman, R. J. Doedens, *Inorg. Chem.* **1983**, *22*, 1591; b) M. Nakashima, M. Mikuriya, Y. Muto, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 968; c) Y. Muto, A. Sasaki, T. Tokii, M. Nakashima, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2572; d) J. Barluenga, L. A. López, O. Löber, M. Tomás, S. García-Granda, C. Alvarez-Rúa, J. Borge, *Angew. Chem. Int. Ed.* **2001**, *40*, 3392; *Angew. Chem.* **2001**, *113*, 3495; e) J. Irangu, M. J. Ferguson, R. B. Jordan, *Inorg. Chem.* **2005**, *44*, 1619.

[8] a) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325; b) M. Meldal, C. W. Tornoe, *Chem. Rev.* **2008**, *108*, 2952; c) C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464; d) A. Casitas, X. Ribas, *Chem. Sci.* **2013**, *4*, 2301; e) S. R. Chemler, *Science* **2013**, *341*, 624.

[9] Y. Wei, M. Shi, *Chem. Rev.* **2013**, *113*, 6659.

[10] a) M. Schmittel, A. Haeuseler, *J. Organomet. Chem.* **2002**, *661*, 169; b) T. Amatov, U. Jahn, *Angew. Chem. Int. Ed.* **2011**, *50*, 4542; *Angew. Chem.* **2011**, *123*, 4636.

[11] a) A. J. Kirby, R. Lelain, P. Mason, F. Maharlouie, P. J. Nicholls, H. J. Smith, C. Simons, *J. Enzyme Inhib. Med. Chem.* **2002**, *17*, 321; b) S.-C. Chien, M.-L. Chen, *J. Agric. Food Chem.* **2008**, *56*, 7017; c) K. Kaminski, J. Obniska, *Bioorg. Med. Chem.* **2008**, *16*, 4921.

[12] CCDC 932845 (**3aa**), 946349 (**3na**), and 932846 (**5aa**) 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.

[13] a) V. K. Aggarwal, A. Mereu, G. J. Tarver, R. McCague, *J. Org. Chem.* **1998**, *63*, 7183; b) R. Lee, F. Zhong, B. Zheng, Y. Meng, Y. Lu, K. Huang, *Org. Biomol. Chem.* **2013**, *11*, 4818.

[14] G. Micera, S. Deiana, L. Erre, P. Piu, A. Panzanelli, *J. Chem. Educ.* **1984**, *61*, 646.

[15] D. M. Arnott, P. J. Harrison, G. B. Henderson, Z.-C. Sheng, F. J. Leeper, A. R. Battersby, *J. Chem. Soc. Perkin Trans.* **1989**, 265.

[16] The kinetic isotope effects observed in intermolecular competition experiments ($k_H/k_D = 1.52$) suggested that the cleavage of the olefinic C–H bond at the α-position of cinnamic acid is not involved in the rate-limiting step. See the Supporting Information for details.

Received: December 12, 2014
Revised: February 11, 2015