Photochemistry

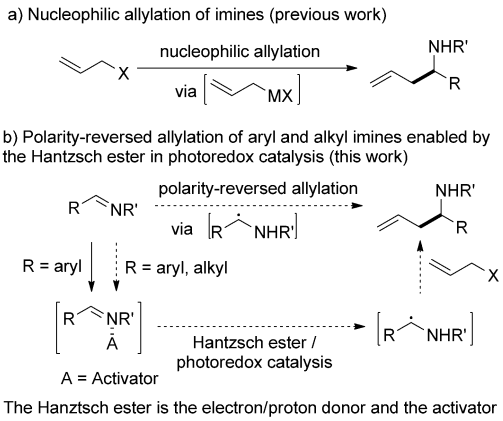
Deutsche Ausgabe: DOI: 10.1002/ange.201607813
Internationale Ausgabe: DOI: 10.1002/anie.201607813

Polarity-Reversed Allylations of Aldehydes, Ketones, and Imines Enabled by Hantzsch Ester in Photoredox Catalysis

*Li Qi and Yiyun Chen**

Abstract: *The polarity reversal (umpolung) reaction is an invaluable tool for reversing the chemical reactivity of carbonyl and iminyl groups, which subsequent cross-coupling reactions to form C–C bonds offers a unique perspective in synthetic planning and implementation. Reported herein is the first visible-light-induced polarity-reversed allylation and intermolecular Michael addition reaction of aldehydes, ketones, and imines. This chemoselective reaction has broad substrate scope and the engagement of alkyl imines is reported for the first time. The mechanistic investigations indicate the formation of ketyl (or α-aminoalkyl) radicals from single-electron reduction, where the Hantzsch ester is crucial as the electron/proton donor and the activator.*

The carbon–heteroatom double bond (such as the carbonyl or the iminyl group) is a valuable synthon for building new carbon–carbon bonds by additive cross-coupling reactions.[1] As both the carbonyl and iminyl groups are polarized and electrophilic, they can easily undergo nucleophilic addition reactions to construct β-functionalized alcohols and amines, respectively (Scheme 1 a).[2] In contrast, its engagement as the nucleophilic equivalent (the ketyl or the α-aminoalkyl radical) requires the use of strong reductants, such as an alkali metal, or titanium and samarium reagents.[3] While widely used, these reductants are water- or air-sensitive, and are incompatible with many sensitive functional groups, which limits their use in increasingly demanding modern organic synthesis and chemical biology studies.[4] Recently, the generation of either ketyl or α-aminoalkyl radicals by photoredox catalysis under mild reaction conditions has been reported.[5,6] However, current applications of visible-light-induced ketyl or α-aminoalkyl radicals in intermolecular cross-coupling reactions are limited to radical–radical coupling reactions, and their use in intermolecular radical addition reactions is unknown.[5,6] In addition, the reduction-resistant alkyl imines (alkyl aldehydes derived imines, $E^0_{1/2} < -3.0$ V vs. SCE in MeCN) do not react under current photoredox methods (Scheme 1 b).[7]



Scheme 1. Nucleophilic and polarity-reversed allylation.

Homoallylic alcohols and amines are pivotal building blocks in organic synthesis, and their traditional syntheses rely on nucleophilic allylations.[8] In contrast, the polarity-reversed allylation of aldehydes, ketones, and imines using ketyl (or α-aminoalkyl) radical is unknown, which would introduce a unique perspective in retrosynthetic analysis and implementations. Herein we report the first visible-light-induced polarity-reversed allylation and intermolecular Michael addition reactions of aldehydes, ketones, and imines, and it is also applicable to alkyl imines for the first time.

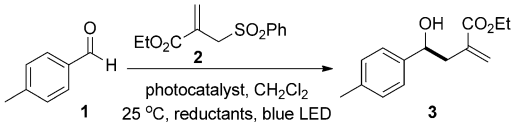
We started our investigation with the readily available *p*-methylbenzaldehyde (**1**) and the allyl sulfone **2** as substrates. Using $[Ru(bpy)_3](PF_6)_2$ ($E^0_{1/2}{}^{II/I} = -1.33$ V vs. SCE in MeCN) under blue LED ($\lambda_{max} = 468 \pm 25$ nm) irradiation,[9] the homoallylic alcohol **3** was obtained in 63% yield with the Hantzsch ester as a reductant (Table 1, entry 1).[10] The use of the iridium-based photocatalyst $[Ir(dtbbpy)(ppy)_2]PF_6$ ($E^0_{1/2}{}^{III/II} = -1.51$ V vs. SCE in MeCN) accelerates the reaction to three hours with 80% yield (entry 2).[11] The addition of diisopropylethylamine further improves the reaction to 90% yield (entry 3). However, the use of diisopropylethylamine alone yields the allylation adduct **3** in merely 28% yield (entry 4). Notably, the addition of water or exposure to air does not affect the reaction (entries 5 and 6).[3] The photocatalyst, light, and reductants are all critical for the reaction (entries 7–9).

We further explored the mechanism of this novel polarity-reversed allylation. The luminescence quenching experiments indicate that either the diisopropylethylamine or the Hantzsch ester quenches the photoexcited $[Ir(dtbbpy)(ppy)_2]PF_6$ effectively, while both **1** and **2** are ineffective.[12] In the absence of **2**, the pinacol-coupling adduct **5** (*dl*/*meso* = 1.5:1) is obtained from the aldehyde **4** in 83% yield (Scheme 2 a). In contrast, in the absence of **1**, little conversion of **2** was observed.[12] These results collectively suggest the formation of ketyl radicals in the photoredox reaction.

[*] L. Qi, Prof. Dr. Y. Chen
State Key Laboratory of Bioorganic and Natural Products Chemistry
Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (China)
E-mail: yiyunchen@sioc.ac.cn

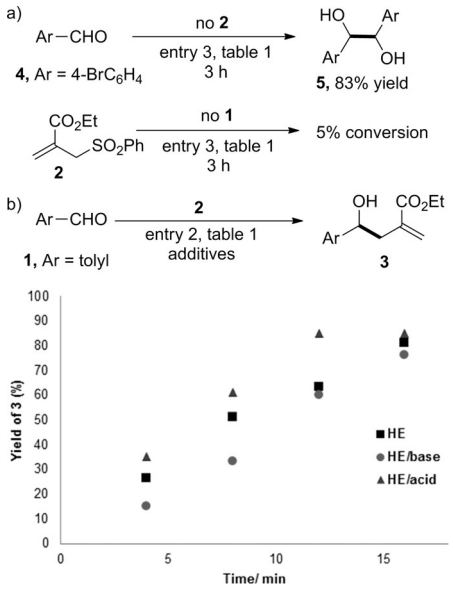
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201607813.

Table 1: Optimization of the aldehyde allylation reaction.



Entry	Reaction conditions[a]	t [h]	Conv. [%][b]	Yield [%][b]
1	$[Ru(bpy)_3](PF_6)_2$, HE	24	>95	63
2	$[Ir(dtbbpy)(ppy)_2]PF_6$, HE	3	>95	80 (73)
3	$[Ir(dtbbpy)(ppy)_2]PF_6$, HE, iPr$_2$NEt	3	>95	90 (84)
4	$[Ir(dtbbpy)(ppy)_2]PF_6$, iPr$_2$NEt	3	30	28
5	entry 3, CH_3CN/H_2O	3	>95	99
6	entry 3, air	3	>95	91
7	entry 3, no HE/iPr$_2$NEt	3	<5	0
8	entry 3, no $h\nu$	3	<5	0
9	entry 3, no [Ir]	24	<5	0

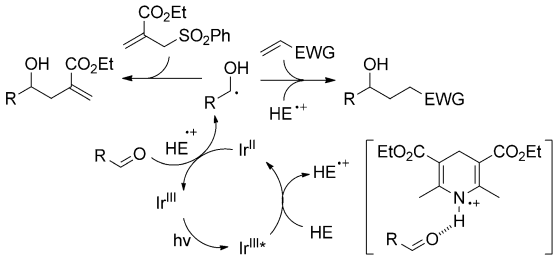
[a] Reaction conditions: **1** (0.10 mmol), **2** (0.30 mmol), photocatalyst (0.001 mmol), Hantzsch ester (HE, 0.15 mmol), and iPr$_2$NEt (0.20 mmol) in 1.0 mL dichloromethane under nitrogen with 468 nm LED irradiation. [b] Conversions and yields were determined by ^{1}H NMR analysis. Yields of isolated products given within parentheses. dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine, ppy = 2-phenylpyridine.



Scheme 2. Mechanistic investigations of the polarity-reversed allylation reaction.

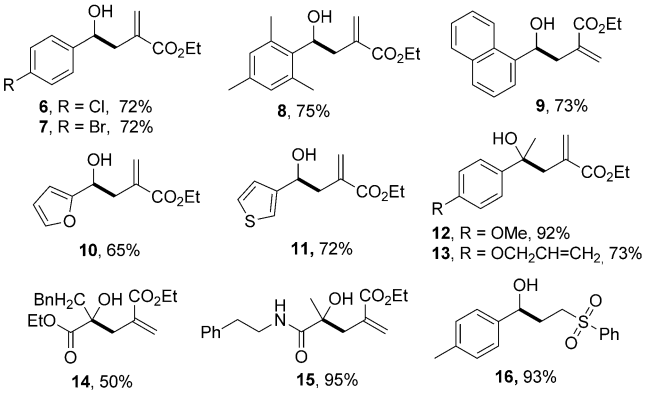
However, it is puzzling how the electron transfer occurs with aldehydes. With the very low aldehyde reduction potentials ($E^0_{1/2} = -2.28$ V vs. SCE in MeCN for **1**),[13] neither the photoexcited $[Ir(dtbbpy)(ppy)_2]PF_6$ (III)* ($E^0_{1/2}{}^{IV/III*} = -0.96$ V vs. SCE in MeCN) nor the reductive $[Ir(dtbbpy)(ppy)_2]PF_6$ (II) ($E^0_{1/2}{}^{III/II} = -1.51$ V vs. SCE in MeCN) is suitable for reduction.[11] Previous reports of visible-light-induced ketyl radical formation uses Lewis acids or in situ generated acids to facilitate the electron transfer, and those reactions are enhanced by the addition of acids and inhibited by the addition of bases.[5,6] We then did the acid/base doping experiments with only the Hantzsch ester as a reductant (Scheme 2b). The acid (acetic acid; triangles) accelerates the reaction compared to the reaction without additives (squares), and the base (sodium carbonate; circles) decelerates the reaction. While it is unclear at this point how the Hantzsch ester activates the aldehyde, the Hantzsch ester radical cation formed during the oxidation might activate the aldehyde by the proton-coupled electron-transfer (PCET) mechanism.[5,6,14]

Based on mechanistic investigations above, we propose that $[Ir(dtbbpy)(ppy)_2]PF_6$ is photoexcited to Ir^{III}* and reduced by the Hantzsch ester to Ir^{II} (Scheme 3). The resulting Ir^{II} intermediate reduces the aldehydes by single-electron transfer with the activation from the Hantzsch ester radical cation.[14] With the proton transfer from the Hantzsch ester radical cation, the hydroxymethyl radical then adds either to the allyl sulfone to obtain the homoallylic alcohol or to the Michael acceptor to obtain the Michael addition adduct.[15] In the photoredox system, the Hantzsch ester is crucial as electron/proton donor, and also serves to activate the aldehydes.



Scheme 3. Mechanistic proposal of the polarity-reversed allylation reaction. EWG = electron-withdrawing group.

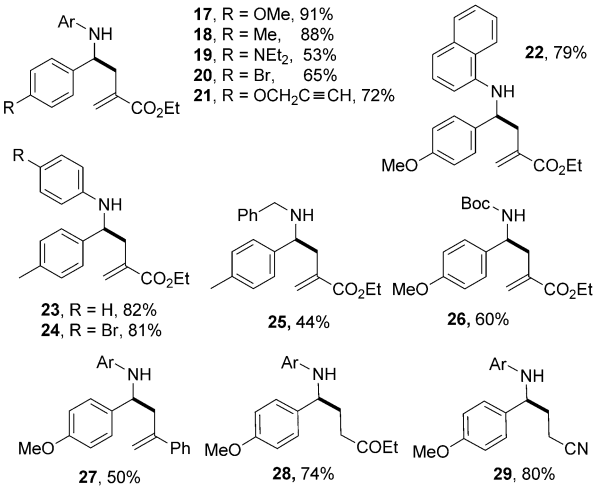
With the mild polarity-reversal reaction conditions in hand (entry 3 in Table 1),[16] we explored the substrate scope with respect to the aldehydes and ketones. Halogen substituents on the benzaldehydes did not affect the reaction, and delivered the chloro- and bromo-substituted homoallylic alcohols **6** and **7**, respectively, in 72% yield (Scheme 4). The bulky mesityl- and naphthyl-substituted aldehydes reacted



Scheme 4. Substrate scope with respect to aldehydes and ketones. Reaction conditions are those detailed in entry 3 of Table 1. Yield is that of isolated product.

smoothly to deliver **8** (75%) and **9** (73%), respectively. Heterocycles are well tolerated to give the furan- and thiophene-containing homoallylic alcohols **10** (65%) and **11** (72%), respectively. This reaction works with arylketones to give the homoallylic tertiary alcohols **12** (92%) and **13** (73%), in which the allylic ether group is not affected. Ester- and amide-substituted ketones selectively yielded the ketone allylation adducts **14** and **15**, respectively, without affecting either the ester or the amide group.[17] The ketyl radical can engage in radical additions other than allylation as indicated by the Michael addition adduct **16**, which is effectively obtained in 93% yield by reaction with vinyl sulfones.

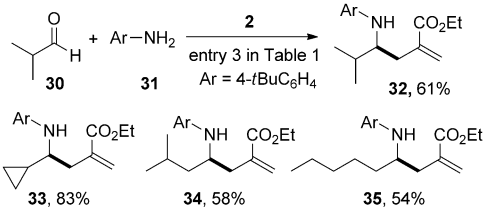
We next tested the aryl imines in our reaction conditions, as they were less studied in polarity reversal reactions because of the low reactivity.[1c,6] With the 4-tertbutylaniline-derived aryl imine, various substitutions including the methyl, methoxy, and diethylamino, as well as the bromo group all react well to give **17**–**20** in 53–91% yields (Scheme 5). The



Scheme 5. Substrate scope of aryl imines. Reaction conditions are those detailed in entry 3 of Table 1. Yield is that of isolated product. Ar = 4-*t*BuC$_6$H$_4$. Boc = *tert*-butoxycarbonyl.

propargyl ether group is tolerated to give **21** in 72% yield. 1-Naphthylamine and various anilines reacted smoothly to give **22**–**24** in 79–82% yields. The imine is not limited to aniline derivatives as benzylamine and Boc-amine-derived imines also reacted, albeit in slightly decreased yields, to give **25** and **26** smoothly. This reaction is also applicable to non-electron-withdrawing allyl acceptors and the styrene derivative **27** can be obtained in a slightly decreased 50% yield. The α-aminoalkyl radical can also engage in Michael addition reactions with vinyl ketones and nitriles to give **28** (74%) and **29** (80%), respectively.

We lastly tested inherently unstable alkyl imines, which were very difficult to reduce ($E^0_{1/2} < -3.0$ V vs. SCE in MeCN) and were elusive in previous photoredox reactions (Scheme 6).[5,6] We speculated that with the effective reaction conditions and formation of the alkyl imine in situ, this challenging transformation could be achieved. We mixed the



Scheme 6. Three-component reaction of alkyl imines.

isobutylaldehyde (**30**) and 4-*tert*-butylaniline (**31**) together with **2** under the photoredox reaction conditions, and the homoallylic amine **32** was obtained in 61% yield from the three-component reaction.[18] The cyclopropyl-substituted aldehyde reacts without ring opening to give the homoallylic amine **33** in 83% yield.[19] Isobutyl- or pentyl-substituted aldehydes also reacted smoothly to yield **34** and **35**, respectively, in slightly decreased yields.

In conclusion, we have developed the first visible-light-induced polarity-reversed allylation and intermolecular Michael addition reactions of aldehydes, ketones, and imines with an unprecedented broad substrate scope. The Hantzsch ester is reported for the first time as the activator in the photoredox catalytic system and enables the polarity reversed allylation of alkyl imines. This unique reactivity of the Hantzsch ester in photoredox catalysis and its application for biomolecules are under investigation in our laboratory.

Acknowledgments

Financial support was provided by the National Basic Research Program of China (2014CB910304) and the National Natural Science Foundation of China (21272260, 21472230).

Keywords: allylic compounds · iridium · photoredox catalysis · radicals · umpolung

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 13312–13315
Angew. Chem. **2016**, *128*, 13506–13509

[1] a) C. E. Masse, J. S. Panek, *Chem. Rev.* **1995**, *95*, 1293–1316; b) G. K. Friestad, A. K. Mathies, *Tetrahedron* **2007**, *63*, 2541–2569; c) K. Yamada, K. Tomioka, *Chem. Rev.* **2008**, *108*, 2874–2886; d) M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853–2873; e) M. Szostak, N. J. Fazakerley, D. Parmar, D. J. Procter, *Chem. Rev.* **2014**, *114*, 5959–6039.

[2] a) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763–2793; b) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094; c) S. Kobayashi, Y. Mori, J. S. Fossey, M. M. Salter, *Chem. Rev.* **2011**, *111*, 2626–2704.

[3] a) A. Chatterjee, N. N. Joshi, *Tetrahedron* **2006**, *62*, 12137–12158; b) K. C. Nicolaou, S. P. Ellery, J. S. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 7140–7165; *Angew. Chem.* **2009**, *121*, 7276–7301; c) M. Szostak, D. J. Procter, *Angew. Chem. Int. Ed.* **2012**, *51*, 9238–9256; *Angew. Chem.* **2012**, *124*, 9372–9390.

[4] a) R. A. Shenvi, D. P. O'Malley, P. S. Baran, *Acc. Chem. Res.* **2009**, *42*, 530–541; b) N. A. Afagh, A. K. Yudin, *Angew. Chem. Int. Ed.* **2010**, *49*, 262–310; *Angew. Chem.* **2010**, *122*, 270–320;

c) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004; *Angew. Chem.* **2001**, *113*, 2056; d) E. M. Sletten, C. R. Bertozzi, *Angew. Chem. Int. Ed.* **2009**, *48*, 6974 – 6998; *Angew. Chem.* **2009**, *121*, 7108 – 7133.

[5] Pioneering work of ketyl radical formation by photoredox catalysis and their application to intramolecular rearrangement/addition reactions: a) M. H. Larraufie, R. Pellet, L. Fensterbank, J. P. Goddard, E. Lacôte, M. Malacria, C. Ollivier, *Angew. Chem. Int. Ed.* **2011**, *50*, 4463 – 4466; *Angew. Chem.* **2011**, *123*, 4555 – 4558; b) K. T. Tarantino, P. Liu, R. R. Knowles, *J. Am. Chem. Soc.* **2013**, *135*, 10022; c) L. J. Rono, H. G. Yayla, D. Y. Wang, M. F. Armstrong, R. R. Knowles, *J. Am. Chem. Soc.* **2013**, *135*, 17735.

[6] The use of ketyl or α-aminoalkyl radicals by photoredox catalysis in radical–radical coupling reactions have been reported: a) F. R. Petronijević, M. Nappi, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 18323; b) M. Nakajima, E. Fava, S. Loescher, Z. Jiang, M. Rueping, *Angew. Chem. Int. Ed.* **2015**, *54*, 8828; *Angew. Chem.* **2015**, *127*, 8952; c) J. L. Jeffrey, F. R. Petronijević, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 8404; d) D. Uraguchi, N. Kinoshita, T. Kizu, T. Ooi, *J. Am. Chem. Soc.* **2015**, *137*, 13768; e) C. Y. Wang, J. Qin, X. D. Shen, R. Riedel, K. Harms, E. Meggers, *Angew. Chem. Int. Ed.* **2016**, *55*, 685; *Angew. Chem.* **2016**, *128*, 695; f) E. Fava, A. Millet, M. Nakajima, S. Loescher, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, *55*, 6776; *Angew. Chem.* **2016**, *128*, 6888.

[7] a) R. W. Layer, *Chem. Rev.* **1963**, *63*, 489; b) D. K. Root, W. H. Smith, *J. Electrochem. Soc.* **1982**, *129*, 1231.

[8] a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207 – 2293; b) G. K. Friestad, H. Ding, *Synthesis* **2005**, 2815 – 2829; c) M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2011**, *111*, 7774 – 7854.

[9] A. Juris, V. Balzani, F. Barigelletti, S. Campagna, P. Belser, A. Vonzelewsky, *Coord. Chem. Rev.* **1988**, *84*, 85 – 277.

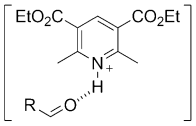
[10] The use of the Hantzsch ester as both the electron and proton donor in photoredox catalysis has been reported before: see Ref. [5a] and J. Zhang, Y. Li, F. Y. Zhang, C. C. Hu, Y. Y. Chen, *Angew. Chem. Int. Ed.* **2016**, *55*, 1872 – 1875; *Angew. Chem.* **2016**, *128*, 1904 – 1907.

[11] M. S. Lowry, J. I. Goldsmith, J. D. Slinker, R. Rohl, R. A. Pascal, G. G. Malliaras, S. Bernhard, *Chem. Mater.* **2005**, *17*, 5712 – 5719.

[12] See the Supporting Information for details.

[13] F. Amemiya, K. Fuse, T. Fuchigami, M. Atobe, *Chem. Commun.* **2010**, *46*, 2730.

[14] The oxidized Hantzsch ester cation may also activate the aldehydes. See the Supporting Information for details. Similar carbonyl group activation examples by tertiary amine cations: a) T. Schuster, M. Kurz, M. W. Göbel, *J. Org. Chem.* **2000**, *65*, 1697; b) J. Kadota, D. Pavlović, J. P. Desvergne, B. Bibal, F. Peruch, A. Deffieux, *Macromolecules* **2010**, *43*, 8874; and Ref. [6b].



[15] It is unclear at this point if the the hydroxymethyl radical (or the ketyl radical anion) adds to the allyl sulfone and Michael acceptor. The reaction is light-dependent as observed by the on-off light experiment, and the quantum yield of the reaction is 0.8. The radical-chain mechanism is unlikely, however we cannot exclude a possible radical-chain mechanism with very short chain length. See the Supporting Information for details.

[16] The reaction conditions of entry 5 in Table 1 was not used as many imines were not stable in water and many substrates were not soluble in water cosolvent.

[17] M. Szostak, M. Spain, D. J. Procter, *Chem. Soc. Rev.* **2013**, *42*, 9155 – 9183.

[18] The alkyl aldehyde is not reactive in the polarity-reversal reaction conditions.

[19] The ring opening of the cyclopropyl ketyl radical anion is much slower than that of the cyclopropyl radical, see: a) J. M. Tanko, R. E. Drumright, *J. Am. Chem. Soc.* **1990**, *112*, 5362; b) J. M. Tanko, R. E. Drumright, *J. Am. Chem. Soc.* **1992**, *114*, 1844; The stabilization of cyclopropyl radical has been reported with either an α-nitrogen or oxygen atom, see: c) D. D. M. Wayner, K. B. Clark, A. Rauk, D. Yu, D. A. Armstrong, *J. Am. Chem. Soc.* **1997**, *119*, 8925.

Received: August 11, 2016
Published online: September 20, 2016

