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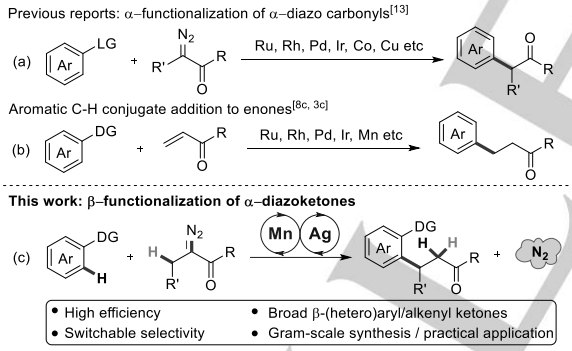
Mn(I)/Ag(I) Relay Catalysis: Traceless Diazo-Assisted C(sp²)–H/C(sp³)–H Coupling to β-(Hetero)Aryl/Alkenyl Ketones

Qingquan Lu, Shobhan Mondal, Sara Cembellín and Frank Glorius*

Dedicated to Prof. Xiyan Lu on the occasion of his 90th birthday

Abstract: An unprecedented Mn(I)/Ag(I) relay-catalyzed C(sp²)–H/C(sp³)–H coupling of (vinyl)arenes with α-diazoketones is reported, wherein the diazo group was exploited as a traceless auxiliary for control of regioselectivity. Challenging β-(hetero)aryl/alkenyl ketones were obtained via this operationally simple approach. The cascade process merges denitrogenation, carbene rearrangement, C–H activation and hydroarylation/hydroalkenylation. The robustness of this methodology was exhibited at preparative scale and applied to late-stage diversification of natural products.

C–H bond activation has become one of the most powerful methods to access valuable molecules from readily available hydrocarbons.[1] In this regard, the pursuit of more sustainable, efficient catalyst systems has been of long-standing interest. Distinct catalyst systems employing manganese, an abundant, economical and low toxicity transition metal, have received great attention and been developed by the groups of Kuninobu and Takai,[2] Wang,[3] Ackermann,[4] Glorius[5] and others.[6] Despite these major advances, discovery of novel manganese systems and site-selective C–H/C–H crossing coupling reactions remain an extremely attractive yet challenging goal.



Scheme 1. Mn(I)/Ag(I) relay-catalyzed C(sp²)–H/C(sp³)–H coupling.

β-(Hetero)aryl ketones are prevalent structural motifs in pesticides, anti-oxidants, and drug candidates.[7] Typically, they are obtained by conjugate addition of aryl-metal species to enones.[8] However, enones (especially of alkyl enones), which are often derived from their saturated analogues using stoichiometric oxidants,[9] are limited to terminal/activated enones or 2-cyclohexenone/2-cyclopentenone derivatives in most of reported methods.[8] Transition-metal-catalyzed tandem ketone dehydrogenation and conjugate addition has emerged as an alternative.[7, 10] While β-arylation of cyclohexanone derivatives with aryl halides or aryl-metal reagents is known, derivatization of linear ketones and macrocyclic ketones remains challenging. Furthermore, necessity of air-sensitive ligands and stoichiometric oxidants decreases practicality of these reactions.[7, 10] Therefore, it is highly desirable to find new strategies to access these compounds.[11]

Diazo compounds can be easily prepared from the corresponding ketones and are widely used in organic synthesis.[12] In principle, they are known to react with organometallic species to generate metal carbene intermediates, which in turn undergo rapid migratory insertion to furnish alkylated products (Scheme 1a, LG: leaving group).[13] This general protocol has been extensively explored using Ir, Pd, Rh, Ru, Co, Cu etc, whereas Mn has been seldom studied in this area.[13] Additionally, the Wang group has developed a pioneering amine-accelerated Mn-catalyzed aromatic C–H conjugate addition to α,β-unsaturated carbonyls (Scheme 1b).[3c] Compared with acrylates, enones showed much lower reactivity in this protocol. Furthermore, presumably owing to predominately undesired β-H elimination of alkyl–M species formed by migratory insertion of carbene into C–M bond, activation of a C(sp³)–H bond of diazo compounds remains largely undeveloped. On this basis, we reasoned that the remarkable difficulty of β-H elimination observed in manganese catalysis might offer a new pathway to overcome these limitations.[14] Herein, we describe a novel Mn(I)/Ag(I) relay catalysis that enables formal C(sp²)–H/C(sp³)–H coupling to generate β-(hetero)aryl/alkenyl ketones with exclusive regioselectivity, in which α-diazoketones were used as ketone equivalents (Scheme 1c). This operationally simple approach is highly effective with previously challenging linear and macrocyclic ketones, including unbiased dialkyl ketones, exhibiting switchable selectivity.

To probe the feasibility of our assumption, we initially chose *N*-(2-pyridyl)indole (**1a**) and 2-diazo-1-phenylpropan-1-one (**2a)** as the standard substrates. After extensive screening of various reaction parameters, it was found that the combination of commercially available $MnBr(CO)_5$ and $AgBF_4$ could offer the formal C(sp²)–H/C(sp³)–H coupling product **3aa** in almost quantitative yield (Scheme 2),[15] with β-site selectivity of α-diazoketone being in contrast with previous reports using diazo compound as reactant.[16]

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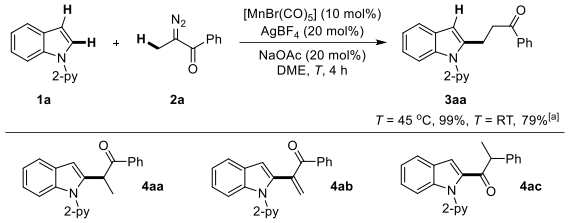
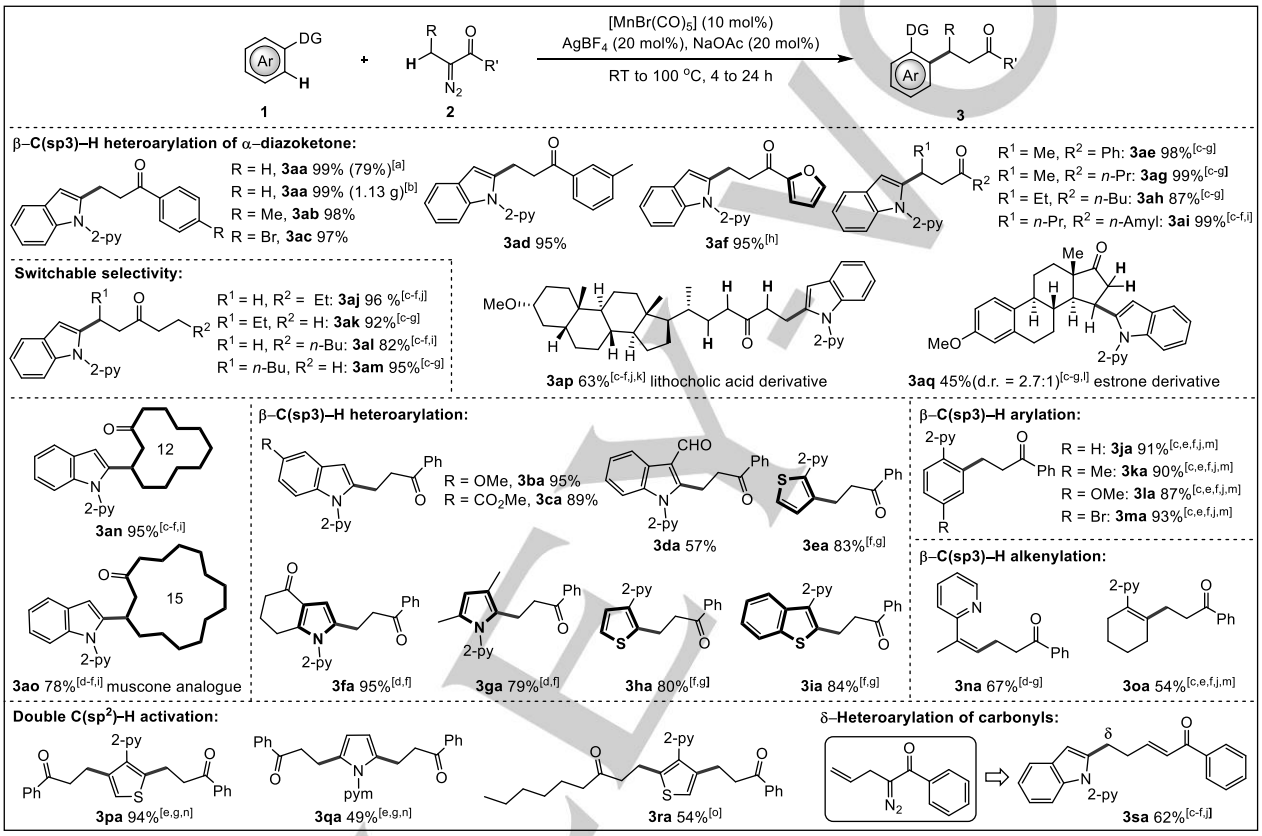


Scheme 2. All reactions were carried out using **1a** (0.20 mmol), **2** (1.2 equiv.), $[MnBr(CO)_5]$ (10 mol%), $AgBF_4$ (20 mol%) and NaOAc (20 mol%) in DME (1.0 mL) under argon for 4 h, isolated yield. [a] 24 h.

The classical pathways such as the migratory insertion of carbene into C–Mn bond and subsequent β-H elimination was completely avoided, neither alkylated product **4aa** nor alkenylated product **4ab** was detected. Moreover, **4ac**, which might be formed via the reaction of manganacycle with the Wolff rearrangement of **2a**,[17] was not observed, highlighting the high selectivity of this reaction. Notably, this transformation can also proceed efficiently at room temperature. Control experiments showed that no product was observed in the absence of either $MnBr(CO)_5$ or $AgBF_4$, demonstrating the cooperativity of these catalysts.



Scheme 3. Unless otherwise specified, all reactions were performed with **1** (1.0 equiv.), **2** (1.2 equiv.), $[MnBr(CO)_5]$ (10 mol%), $AgBF_4$ (20 mol%) and NaOAc (20 mol%) in DME (0.2 M) at 45 °C under argon for 4 h, isolated yields. [a] RT, 24 h; [b] 12 h, DME (0.23 M); [c] **2** (1.5 equiv.); [d] BPh_3 (20 mol%); [e] dioxane (0.2 M); [f] 16 h; [g] 80 °C; [h] 5 h; [i] 90 °C; [j] 100 °C; [k] 14 h; [l] dioxane (0.1 M); [m] $[MnBr(CO)_5]$ (15 mol%), $AgBF_4$ (25 mol%), NaOAc (30 mol%), BPh_3 (30 mol%); [n] **2** (2.5 equiv.), $[MnBr(CO)_5]$ (20 mol%), $AgBF_4$ (40 mol%), NaOAc (40 mol%), BPh_3 (40 mol%), 24 h; [o] step 1: **2** (1.15 equiv.) and [d-g] was used, step 2: [c-g] was used.

With the optimized reaction conditions in hand, the generality of this protocol was first investigated by the reaction of **1a** with α-diazo ketones. A series of alkyl-substituted, aryl α-diazoketones were viable in this transformation, providing the desired β-heteroaryl ketones (**3aa**-**3ae**) in 95% to 99% yields. The tolerance of bromide makes this transformation orthogonal to traditional cross-coupling. A heteroaromatic α-diazoketone, 2-diazo-1-(furan-2-yl)propan-1-one, was also found to be a suitable reaction partner in this protocol (**3af**). Although 1,2-dialkyl α-diazoketones have multiple reaction sites, reactions occurred exclusively on the diazo group assisted β-position over reactive acidic α-C–H bonds, giving the corresponding product in excellent yield (**3ag**-**3ao**). In addition, the generality of this protocol was demonstrated by its compatibility with 1,2-dialkyl α-diazoketones prepared from unbiased dialkyl ketones. It addressed the challenging β-functionalization of simple ketones and provided an array of β-heteroaryl ketones (**3aj**-**3am**) in excellent yields with switchable selectivity. Cyclic α-diazoketones, especially for the medium to macrocyclic α-diazoketones, were also successfully β-heteroarylated with **1a**, providing **3an** and **3ao** (the latter being a Muscone analogue) in 95% and 78% yields respectively. Notably, muscone is the main component of musk, which requires a five-step synthesis previously for its preparation from the same ketone in lower yield.[18] To further test the practicability of this reaction, the late-stage manipulation of lithocholic acid and estrone derivatives were successfully demonstrated. Heterocycles, such

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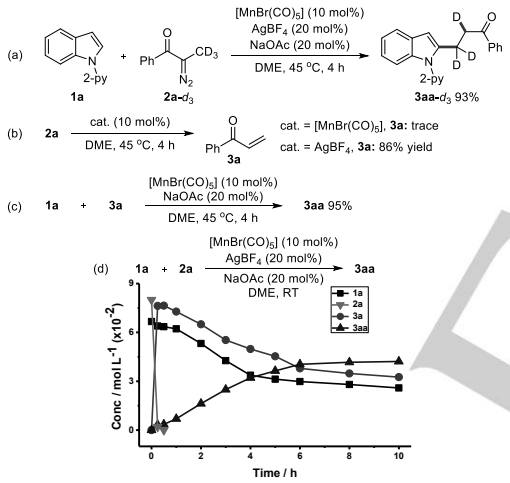
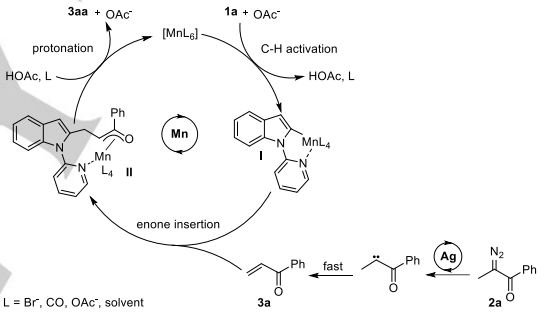
as indoles, thiophenes, benzothiophene and pyrroles, were tolerated in this protocol and gave the β-heteroaryl ketones **3ba**-**3ia** in good to excellent yields. This protocol was also amenable to 2-phenylpyridines, furnishing the corresponding β-aryl ketones **3ja**-**3ma** in 87%-93% yields. Olefinic C–H activation was also achieved by this protocol. The desired β-alkenyl ketones **3na** and **3oa**, with a valuable allyl group for further derivatization, were obtained in 67% and 54% yields respectively. Interestingly, double C–H activation products **3pa** and **3qa** can also be obtained in 94% and 49% yields. Furthermore, a stepwise C(sp^2)–H/C(sp^3)–H coupling of 2-(thiophen-3-yl)pyridine with two α-diazoketones provided the desired product **3ra** in 54% yield. More generally, this approach could be extended to δ-heteroarylation of an α-diazoketone, for example, **3sa** could be obtained in moderate yield.[19] It is noteworthy that this protocol can be readily scaled up to gram quantities with high efficiency. For instance, 1.13 g of the β-heteroaryl ketone **3aa** was isolated in 99% yield without sacrificing the yield. Notably, the loading of manganese catalyst and silver salt can be decreased to 2.5 mol% and 5 mol%, respectively, furnishing the desired product **3aa** in 90% yield (for details, see the SI).



Scheme 4. Mechanistic studies.

To gain insight into the reaction mechanism, a series of experiments were conducted (for details, see the SI). First, H/D scrambling experiments revealed that C–H activation step is reversible and might occur via a base-assisted cyclometalation process. Moreover, $AgBF_4$ did not activate the C–H bond and its presence did not affect the Mn-catalyzed C–H activation step. Furthermore, a minor kinetic isotope effect (k_H/k_D = 1.29) was observed from parallel reactions of **1a** and [D]-**1a** with **2a**, indicating that cleavage of C–H bond is unlikely to be involved in the rate-determining step. In addition, an isotope labeling experiment elucidated that the hydrogen atom in the product **3aa** originates from α-diazoketone **2a** (Scheme 4a). Subsequently, methyl diazoacetoacetate and aryl diazoester, which have been reported to form metal carbene intermediates in transition metal-catalyzed C–H activation,[16c, 16d] were used to determine whether a manganese carbene was involved in this reaction. However, no alkylated product was detected, suggesting that formation of manganese carbene might be unfavourable under this condition.

The interaction of manganese and silver with **2a** was further explored. It was found that 1-phenylprop-2-en-1-one **3a** was generated in 86% yield when **2a** was directly treated with 10 mol% $AgBF_4$, and only a trace amount of **3a** was observed in the presence of $MnBr(CO)_5$ (Scheme 4b). Moreover, **3a**-d_3 was observed when **2a**-d_3 was used in the silver-catalyzed reaction (for details, see the SI), clearly showing that a 1,2-hydrogen migration process was involved.[20] Next, employing **3a** under the standard reaction conditions also afforded **3aa** in 95% yield, indicating that **3a** might be an intermediate (Scheme 4c). We next attempted to use gas chromatography to monitor the reaction between **1a** and **2a**. The kinetic profiles (Scheme 4d) clearly showed that **2a** was fully consumed within 30 min, and **3a** was formed simultaneously. Afterwards, the desired product **3aa** increased gradually in intensity with the consumption of **3a**. These results demonstrated that this transformation proceeds via a tandem denitrogenation-carbene rearrangement-hydroarylation/C–H activation sequence. Additionally, intermolecular competition experiments showed that electron-rich indole and electron-deficient α-diazoketone were more reactive in this transformation.



Scheme 5. Proposed mechanism.

Based on the aforementioned results and previous studies,[14, 20] a mechanism was proposed in Scheme 5. A silver-catalyzed, denitrogenation-carbene rearrangement of **2a** generates **3a**. Meanwhile, base-assisted cyclomanganation of **1a** gives an organomanganese specie, which is followed by enone insertion and subsequent protonation to liberate desired β-aryl ketone. The fast 1,2-hydrogen migration, but slower carbene migratory insertion, β-H elimination and unfavourable Wolff rearrangement ensures high reaction selectivity, enabling the facile synthesis of structurally diverse β-aryl/alkenyl ketones.

In summary, we have developed a new approach to the synthesis of β-(hetero)aryl/alkenyl ketones via Mn(I)/Ag(I) relay catalysis, many of which are difficult to access using previously reported methods. This unique strategy opens up a new channel to couple metal-catalyzed C–H activation with β-C(sp^3)–H functionalization of α-diazoketone, which can be performed on a broad substrate scope derived from diverse ketones.

Keywords: manganese • C−H activation • relay catalysis • β-heteroaryl ketone • α-diazoketone

[1] Selected reviews, see: a) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074 – 1086; b) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624 – 655; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147 – 1169; d) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315 – 1345; e) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068 – 5083; f) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885 – 1898; g) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 3362 – 3374; *Angew. Chem*. **2011**, *123*, 3422 – 3435; h) C. L. Sun, B. J. Li, Z. J. Shi, *Chem. Rev.* **2011**, *111*, 1293 – 1314; i) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215 – 1292; j) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788 – 802; k) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960 – 9009; *Angew. Chem*. **2012**, *124*, 9092 – 9142; l) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053 – 1064.

[2] a) Y. Kuninobu, Y. Nishina, T. Takeuchi, K. Takai, *Angew. Chem. Int. Ed.* **2007**, *46*, 6518 – 6520; *Angew. Chem*. **2007**, *119*, 6638 – 6640; b) S. Sueki, Z. Wang, Y. Kuninobu, *Org. Lett.* **2016**, *18*, 304 – 307.

[3] a) B. Zhou, H. Chen, C. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 1264 – 1267; b) R. He, Z. T. Huang, Q. Y. Zheng, C. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 4950 – 4953; *Angew. Chem*. **2014**, *126*, 5050 – 5053; c) B. Zhou, P. Ma, H. Chen, C. Wang, *Chem. Commun.* **2014**, *50*, 14558 – 14561; d) B. Zhou, Y. Hu, C. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 13659 – 13663; *Angew. Chem*. **2015**, 127, 13863 – 13867; e) Y. Hu, C. Wang, *Sci. China Chem.* **2016**, *59*, 1301 – 1305; f) X. Yang, X. Jin, C. Wang, *Adv. Synth. Catal.* **2016**, *358*, 2436 – 2442; g) B. Zhou, Y. Hu, T. Liu, C. Wang, *Nat. Commun.* **2017**, | 8: 1169; h) X. Yang, C. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 923 – 928; *Angew. Chem*. **2018**, 130, 935 – 940.

[4] a) W. Liu, J. Bang, Y. Zhang, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 14137 – 14140; *Angew. Chem*. **2015**, *127*, 14343 – 14346; b) W. Liu, D. Zell, M. John, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 4092 – 4096; *Angew. Chem*. **2015**, 127, 4165 – 4169; c) W. Liu, S. C. Richter, Y. Zhang, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 7747 – 7750; *Angew. Chem*. **2016**, *128*, 7878–7881; d) Y.-F. Liang, V. Müller, W. Liu, A. Münch, D. Stalke, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 9415 – 9419; *Angew. Chem.* **2017**, *129*, 9543 – 9547; e) Z. Ruan, N. Sauermann, E. Manoni, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 3172 – 3176; *Angew. Chem.* **2017**, *129*, 3220 – 3224; f) H. Wang, M. M. Lorion, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 6339 – 6342; *Angew. Chem.* **2017**, *129*, 6436 – 6439; g) H. Wang, F. Pesciaioli, J. C. A. Oliveira, S. Warratz, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 15063 – 15067; *Angew. Chem.* **2017**, *129*, 15259 – 15263; h) D. Zell, U. Dhawa, V. Müller, M. Bursch, S. Grimme, L. Ackermann, *ACS Catal.* **2017**, *7*, 4209 – 4213.

[5] a) Q. Lu, S. Greßies, S. Cembellín, F. J. R. Klauck, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2017**, *56*, 12778 – 12782; *Angew. Chem.* **2017**, *129*, 12954 – 12958; b) Q. Lu, S. Greßies, F. J. R. Klauck, F. Glorius, *Angew. Chem. Int. Ed.* **2017**, *56*, 6660 – 6664; *Angew. Chem.* **2017**, *129*, 6760 – 6764; c) Q. Lu, F. J. R. Klauck, F. Glorius, *Chem. Sci.* **2017**, *8*, 3379 – 3383; d) Q. Lu, S. Cembellín, S. Greßies, S. Singha, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2018**, *57*, 1399 – 1403; *Angew. Chem.* **2018**, *130*, 1413 – 1417; e) C. Zhu, J. L. Schwarz, S. Cembellín, S. Greßies, F. Glorius, *Angew. Chem. Int. Ed.* **2018**, *57*, 437 – 441; *Angew. Chem.* **2018**, *130,* 445 – 449.

[6] a) L. Shi, X. Zhong, H. She, Z. Lei, F. Li, *Chem. Commun.* **2015**, *51*, 7136 – 7139; b) N. P. Yahaya, K. M. Appleby, M. Teh, C. Wagner, E. Troschke, J. T. W. Bray, S. B. Duckett, L. A. Hammarback, J. S. Ward, J. Milani, N. E. Pridmore, A. C. Whitwood, J. M. Lynam, I. J. S. Fairlamb, *Angew. Chem. Int. Ed.* **2016**, *55*, 12455 – 12459; *Angew. Chem.* **2016**, *128*, 12643-12647; c) S.-H. Cai, L. Ye, D.-X. Wang, Y.-Q. Wang, L.-J. Lai, C. Zhu, C. Feng, T.-P. Loh, *Chem. Commun.* **2017**, *53*, 8731 – 8734; d) S.-Y. Chen, X.-L. Han, J.-Q. Wu, Q. Li, Y. Chen, H. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 9939 – 9943; *Angew. Chem.* **2017**, *129*, 10071 – 10075; e) S.-Y. Chen, Q. Li, X.-G. Liu, J.-Q. Wu, S.-S. Zhang, H. Wang, *ChemSusChem* **2017**, *10*, 2360 – 2364; f) C. Wang, A. Wang, M. Rueping, *Angew. Chem. Int. Ed.* **2017**, *56*, 9935 – 9938; *Angew. Chem*. **2017**, *129*, 10067 – 10070.

[7] Z. Huang, Q. P. Sam, G. Dong, *Chem. Sci.* **2015**, *6*, 5491 – 5498.

[8] a) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829 – 2844; b) A. Gutnov, *Eur. J. Org. Chem.* **2008**, 4547 – 4554; c) L. Yang, H. Huang, *Chem. Rev.* **2015**, *115*, 3468 – 3517.

[9] a) D. R. Buckle, I. L. Pinto, in *Comprehensive Organic Synthesis* (Ed.: I. Fleming), Pergamon, Oxford, **1991**, pp. 119 – 149; b) J. Muzart, *Eur. J. Org. Chem.* **2010**, 3779 – 3790; c) A. Turlik, Y. Chen, T. R. Newhouse, *Synlett* **2016**, *27*, 331 – 336.

[10] a) M. V. Leskinen, K.-T. Yip, A. Valkonen, P. M. Pihko, *J. Am. Chem. Soc.* **2012**, *134*, 5750 – 5753; b) Z. Huang, G. Dong, *J. Am. Chem. Soc.* **2013**, *135*, 17747 – 17750; c) Y. Chen, D. Huang, Y. Zhao, T. R. Newhouse, *Angew. Chem. Int. Ed.* **2017**, *56*, 8258 – 8262; *Angew. Chem.* **2017**, *129*, 8370 – 8374; d) X. Hu, X. Yang, X.-J. Dai, C.-J. Li, *Adv. Synth. Catal.* **2017**, *359*, 2402 – 2406.

[11] a) M. T. Pirnot, D. A. Rankic, D. B. C. Martin, D. W. C. MacMillan, *Science* **2013**, *339*, 1593 – 1596; b) F.-L. Zhang, K. Hong, T.-J. Li, H. Park, J.-Q. Yu, *Science* **2016**, *351*, 252 – 256.

[12] G. Maas, *Angew. Chem. Int. Ed.* **2009**, *48*, 8186 – 8195; *Angew. Chem.* **2009**, *121*, 8332 – 8341.

[13] a) Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* **2013**, *46*, 236 – 247; b) Y. Xia, D. Qiu, J. Wang, *Chem. Rev.* **2017**, *117*, 13810 – 13889.

[14] a) C. Wang, *Synlett* **2013**, *24*, 1606 – 1613; b) W. Liu, L. Ackermann, *ACS Catal.* **2016**, *6*, 3743 – 3752; c) Y. Hu, B. Zhou, C. Wang, *Acc. Chem. Res.* **2018**, *51*, 816 – 827.

[15] CCDC 1828348 (**3aa**) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] a) W.-W. Chan, S.-F. Lo, Z. Zhou, W.-Y. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 13565 – 13568; b) S. Cui, Y. Zhang, D. Wang, Q. Wu, *Chem. Sci.* **2013**, *4*, 3912 – 3916; c) T. K. Hyster, K. E. Ruhl, T. Rovis, *J. Am. Chem. Soc.* **2013**, *135*, 5364 – 5367; d) Z. Shi, D. C. Koester, M. Boultadakis-Arapinis, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 12204 – 12207.

[17] W. Kirmse, *Eur. J. Org. Chem.* **2002**, 2193 – 2256.

[18] B. D. Mookherjee, R. R. Patel, W. O. Ledig, *J. Org. Chem.* **1971**, *36*, 4124 – 4125.

[19] α-Diazoester, as exemplified by ethyl 2-diazopropanoate, showed lower reactivity in this protocol and the corresponding product **3ar** was isolated in 24% yield (for detailes, see the SI).

[20] a)) D. F. Taber, M. J. Hennessy, J. P. Louey, *J. Org. Chem.* **1992**, *57*, 436 – 441; b) D. F. Taber, R. J. Herr, S. K. Pack, J. M. Geremia, *J. Org. Chem.* **1996**, *61*, 2908 – 2910.

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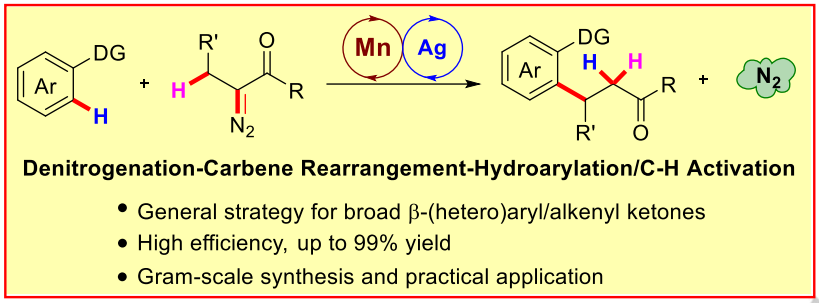

Forward Together! An unprecedented Mn(I)/Ag(I) relay-catalyzed C(sp^2)–H/C(sp^3)–H coupling of (vinyl)arenes with α-diazoketones is reported, wherein diazo group was exploited as traceless auxiliary for control of regioselectivity. This unique strategy opens up a new channel to couple transition metal-catalyzed C–H activation with β-C(sp^3)–H functionalization of α-diazoketone, which efficiently merges denitrogenation, carbene rearrangement, C–H activation and hydroarylation/hydroalkenylation.

*Qingquan Lu, Shobhan Mondal, Sara Cembellín and Frank Glorius**

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Mn(I)/Ag(I) Relay Catalysis: Traceless Diazo-Assisted C(sp^2)–H/C(sp^3)–H Coupling to β-(Hetero)Aryl/Alkenyl Ketones