C–H Activation

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Redox-Neutral Rhodium-Catalyzed C–H Functionalization of Arylamine *N*-Oxides with Diazo Compounds: Primary C(sp^3)–H/C(sp^2)–H Activation and Oxygen-Atom Transfer

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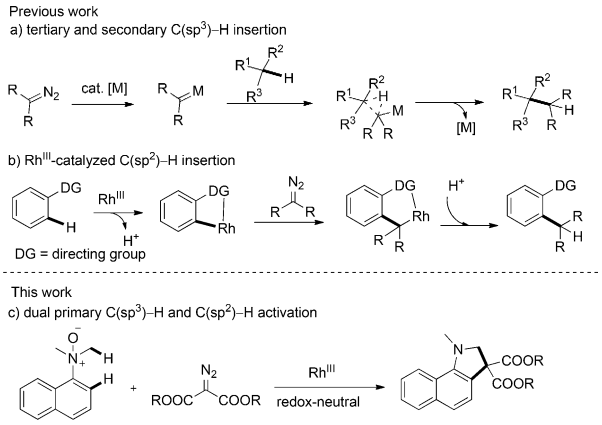
Abstract: *An unprecedented rhodium(III)-catalyzed regioselective redox-neutral annulation reaction of 1-naphthylamine N-oxides with diazo compounds was developed to afford various biologically important 1H-benzo[g]indolines. This coupling reaction proceeds under mild reaction conditions and does not require external oxidants. The only by-products are dinitrogen and water. More significantly, this reaction represents the first example of dual functiaonalization of unactivated a primary C(sp^3)–H bond and C(sp^2)–H bond with diazocarbonyl compounds. DFT calculations revealed that an intermediate iminium is most likely involved in the catalytic cycle. Moreover, a rhodium(III)-catalyzed coupling of readily available tertiary aniline N-oxides with α-diazomalonates was also developed under external oxidant-free conditions to access various aminomandelic acid derivatives by an O-atom-transfer reaction.*



Scheme 1. Transition-metal-catalyzed C–H insertion into α-diazocarbonyl compounds.

Over the past several years, C–H insertion of metal carbenoids has represented an important domain in synthetic methodology for its outstanding advantages in atom and synthesis step efficiency.[1] In this approach, an electron-rich C–H bond generally exhibits higher reactivity toward electrophilic carbene centers, and shows an order of reactivity of tertiary C–H > secondary C–H ≫ primary C–H.[1] Therefore, many studies have been carried out on C(sp^3)–H insertions for tertiary and secondary carbon atoms (Scheme 1a). In sharp contrast, the corresponding intermolecular insertion of C(sp^3)–H (primary) and C(sp^2)–H (aromatic) bonds remains relatively undeveloped and is an important research goal.

Until recently, a rhodium(III)-catalyzed chelation-assisted insertion of aromatic C(sp^2)–H bonds into α-diazocarbonyl compounds have marked a significant breakthrough and emerged as a new approach toward C(sp^2)–H functionalization,[2] and was pioneered by the group of Yu (Scheme 1b).[2a] Mechanistically, the reaction is likely initiated by a chelation-assisted C(sp^2)–H metalation, metal carbene formation, and migratory insertion, and completed by the protonation of the rhodacycle. Despite great progress, this promising C–C coupling reaction is limited to C(sp^2)–H insertion for aromatic centers and the development of new C–C coupling reactions with α-diazocarbonyl compounds [especially by a functionalization of a C(sp^3)–H bond] is still highly desirable.

In contrast, heteroarene *N*-oxides have attracted considerable attention in selective transition-metal-catalyzed C–H bond functionalization by utilizing the *N*-oxide group as a key platform (directing group; DG).[3] Despite significant progress, an additional reducing step was required to reduce the *N*-oxide products. Recently, a redox-neutral process was reported as an attractive alternative in C–H olefination of arylamine *N*-oxides, where the *N*-oxide group acted as both a directing group and internal oxidant, thus obviating the requirement of external oxidants and the additional reducing step.[4] However, to the best of our knowledge, this ideal redox-economic strategy is generally limited to reactions with alkenes.

In this context, we herein report an unprecedented rhodium(III)-catalyzed regioselective redox-neutral annulation of 1-naphthylamine *N*-oxides with diazo compounds to synthesize various 1*H*-benzo[*g*]indolines, which exhibit extraordinary biological and pharmaceutical properties. Examples

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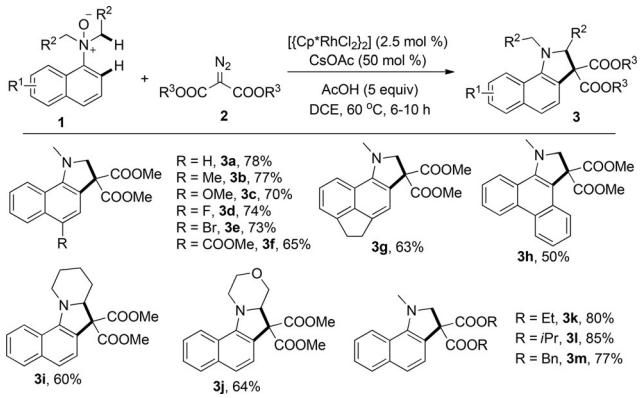
of such compounds are dopamine D2-like receptors, 5-lipoxygenase inhibitor, microsomal PGE2 synthase-1 (mPGES-1) inhibitors, and dyes in zinc oxide dye-sensitized solar cells.[5] More significantly, this reaction represents the first example of the dual functionalization of unactivated primary C(sp^3)–H and C(sp^2)–H bonds with diazocarbonyl compounds (Scheme 1 c).[6]

To begin, *N*,*N*-dimethyl-1-naphthylamine *N*-oxide (**1a**) and diazomalonate (**2a**) were treated with [(Cp*$RhCl_2$)$_2$] (2.5 mol%) and $AgSbF_6$ (10 mol%) in MeOH (2 mL) at 60 °C for 6 hours (see Table S1 in the Supporting Information). Unfortunately, none of the desired product (**3a**; see Scheme 2 for structure) was observed. Given the importance of acetate additives in C–H activations, replacement of the $AgSbF_6$ with CsOAc (50 mol%) or AgOAc (50 mol%) did not give any desired product. Surprisingly, an addition of an acid, AcOH (500 mol%), was found to be crucial for this redox-neutral annulation reaction to provide **3a** in 35% yield. After a screen of solvents, DCE was proven to be optimal, thus providing **3a** in 78% yield.

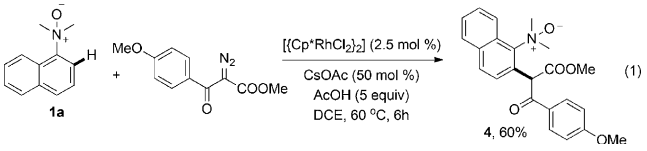
With the optimized reaction conditions in hand, the scope of this methodology was subsequently explored. As shown in Scheme 2, a series of 1*H*-benzo[*g*]indolines were synthesized



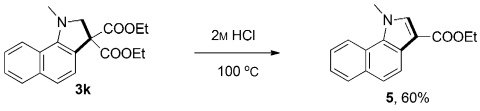
Scheme 2. Rhodium(III)-catalyzed coupling reaction of 1-naphthylamine *N*-oxide with α-diazomalonates. Reaction conditions: 0.2 mmol of **1**, 0.3 mmol of **2**, [{Cp*$RhCl_2$}$_2$] (2.5 mol%), CsOAc (50 mol%), AcOH (500 mol%), DCE (2 mL) at 60 °C for 6 h. Yield of isolated product. Cp* = C_5Me_5, DCE = 1,2-dichloroethane.

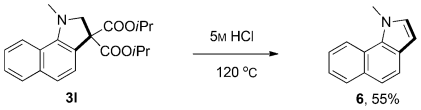
in good yields regardless of whether the *N*,*N*-dimethyl-1-naphthylamine *N*-oxides were electron-rich (**3b**, **3c**, **3g**) or electron-poor (**3d**–**f**). With the assistance of the *N*-oxide group, the C–H bond activation occurred exclusively at the *ortho* postion. Various important functional groups such as methoxy, halogens (F, Br) and ester, were remarkably compatible, thus offering the opportunity for further synthetic transformations. We were pleased to find that this method could also be applied to 9-phenanthrenamine *N*-oxide to give the 1*H*-dibenz[*e*,*g*]indoline **3h**. Besides primary C(sp^3)–H bonds, secondary C(sp^3)–H bonds could also be activated, thus providing the tetracyclic products **3i** and **3j** in moderate yields. Various α-diazomalonates (**3k**–**m**) were also tested under the optimized reaction conditions and coupled smoothly in high yields.

In addition to α-diazomalonates, diazoacetoacetates were also investigated for this coupling reaction. Interestingly, when diazoacetoacetates were used, only the compound **4** was isolated as the sole product in 60% yield [Eq. (1)], presumably because of the higher activity of the rhodacycle intermediate towards protonation. Notably, the C–H bond at the *peri* position of 1-naphthylamine remains untouched[7] and the regioselectivity of this coupling reaction was further confirmed by single-crystal X-ray crystallography.[8] It also merits mentioning that only very limited examples of rhodium(III)-catalyzed functionalization of unactivated C(sp^3)–H bonds have been reported,[9] though rhodium(III)-catalyzed C(sp^2)–H bond functionalization has been explored extensively in the past several years.[10]



To demonstrate the synthetic utility of the current C(sp^2)–H and primary C(sp^3)–H insertion, treatment of the 1*H*-benzo[*g*]indolines product **3k** with aqueous HCl under air resulted in decarbonylation and oxidation to afford the 1*H*-benz[*g*]indole-3-carboxylate **5** in good yield [Eq. (2)].[11] When treating of **3l** with aqueous HCl under air at higher temperature, further decarbonylation occurred to afford the 1*H*-benz[*g*]indole **6** [Eq. (3)].





To probe the reaction mechanism, we treated [D_6]-methyl-*N*,*N*-dimethyl-1-naphthylamine *N*-oxide ([D_6]-**1a**) with **2a** under the standard reaction conditions and no deuterium loss was detected in the product, and is thus indicative of the irreversibility of the C(sp^3)–H bond-cleavage process [Eq. (4)]. Moreover, a kinetic isotope effect (KIE) of 1 was observed in a competitive experiment using equimolar amounts of **1a** and [D_6]-**1a**, thus indicating that the C(sp^3)–H bond cleavage is not involved in the rate-limiting step [Eq. (5)].[12] In addition, a KIE of 3 was observed in a competitive experiment using **1a** and [D_7]-**1a** [Eq. (6)], thus suggesting that the *ortho* C(sp^2)–H bond cleavage might be related to the rate-limiting step.

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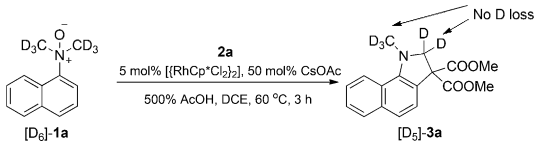

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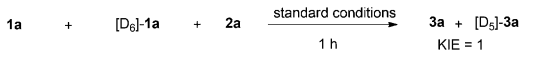

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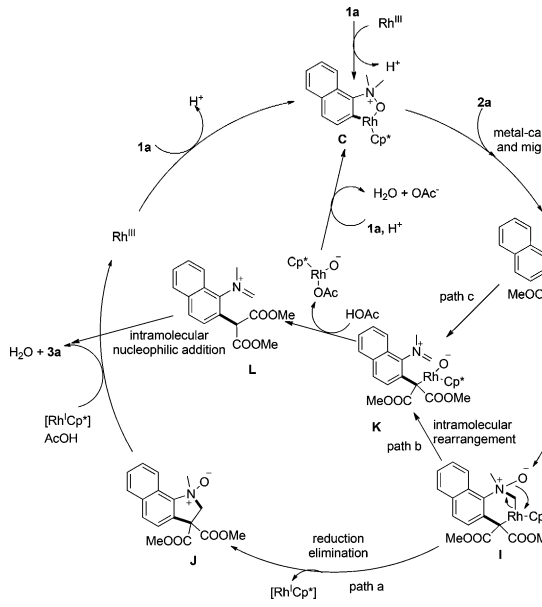
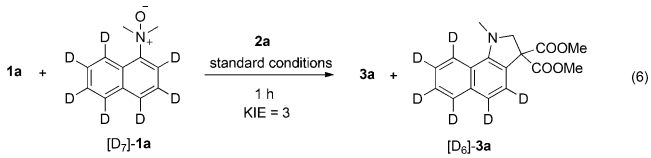


Scheme 3. Proposed mechanism.



(6)

To gain mechanistic details of this dual C(sp^3)–H and C(sp^2)–H insertion reaction, three possible reaction pathways have been proposed (Scheme 3). First, a rhodium(III)-catalyzed reversible *ortho* C–H bond cleavage occurs to form the five-membered rhodacycle **C**.[13] Subsequent coordination of the diazo substrate, followed by an intramolecular 1,2-migratory insertion of the aryl group to afford the six-membered intermediate **H** with extrusion of N_2.[2] In path a, a C(sp^3)–H bond cleavage occurs to provide the rhodacycle **I**. After reductive elimination along with the N–O bond cleavage, the product **3a** was formed and the rhodium(III) catalyst was regenerated. In path b, the rhodacycle **I** may undergo an intramolecular rearrangement to give the intermediate **K**. Then protonation occurs to give the intermediate **L**, which undergoes an enolization of the malonate and an intramolecular nucleophilic addition to iminium to deliver the **3a** as the product. Alternatively, **H** may undergo a Polonovski-type reaction[14] to afford **K** (path c).

To gain further insight into this unprecedented redox-neutral annulation reaction, DFT calculations were performed with Gaussian 09 (see the Supporting Information for details).[15] The energy profiles (free energy and enthalpy) calculated by DFT methods M06 are shown in Figure 1 a. The active catalyst [RhCp*$(OAc)_2$] interacts with **1a** to form **B** and subsequent acetate-assisted C(sp^2)–H activation occurs to give **C** via the transition-state TS-BC, which has an overall free energy of 28.4 kcal mol^{-1}. The coordination of the diazo substrate to **C** forms the intermediate **D** with 12.9 kcal mol^{-1} endothermicity. The subsequent denitrogenation of **D** produces **E** via the transition-state TS-DE with an activation energy barrier of 11.6 kcal mol^{-1}. The Rh–aryl migratory insertion of **E** gives **H** via TS-EH with an activation energy barrier of 5.1 kcal mol^{-1}.

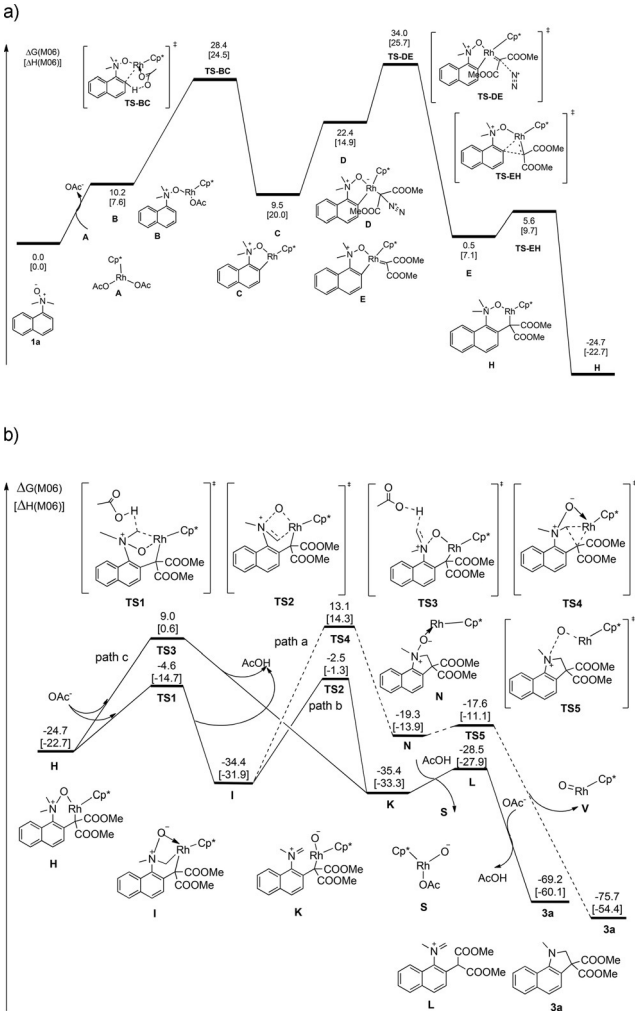


Figure 1. Energy profiles and geometry information for the redox-neutral annulation reactions. The values given by kcal mol^{-1} are the relative free energies calculated by the M06 method in 1,2-dichloroethane as the solvent. The values in square brackets are the enthalpies obtained from the M06 method.

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In path a (Figure 1b), with the assistance of acetate, **H** undergoes a methyl C(sp^3)–H activation, via TS1 with an activation free energy of 20.1 kcal mol^{-1}, to give a more stable complex **I** (9.7 kcal mol^{-1} lower than **H**) with a new C–Rh bond formed. Subsequent C–C reductive elimination of **I** occurs via the transition-state TS4 with an activation free energy of 47.5 kcal mol^{-1}, thus producing the rhodium(I) complex **N**. Finally, oxidation of rhodium(I) with *N*-oxide irreversibly gives the product **3a** via the transition-state TS5, which has a low calculated energy barrier of 1.7 kcal mol^{-1}.

In path b (Figure 1b), **I** undergoes an intramolecular rearrangement to give the iminium **K** via the transition-state TS2, and the calculated free energy of TS2 is 31.9 kcal mol^{-1}, which is 15.6 kcal mol^{-1} lower than that of TS4.[16] Protonolysis of **K** gives **L** which undergoes an intramolecular nucleophilic addition to the iminium to afford **3a** as the product. In comparison with the data in path a, the free energy of **TS2** is 15.6 kcal mol^{-1} lower than that of TS4. Therefore, pathway b is much feasible.

Alternatively, **H** may directly undergo a Polonovski-type reaction to afford **K** via the transition state TS3 with an activation free energy of 33.7 kcal mol^{-1} (path c; Figure 1b). As a summary of our theoretical studies, **K** is most likely involved in the catalytic cycle.

Moreover, we found that the C8–H in the naphthalene ring could stabilize the complex of **H** and acetate by forming a C–H···O interaction (Figure 2),[17] which may be crucial for

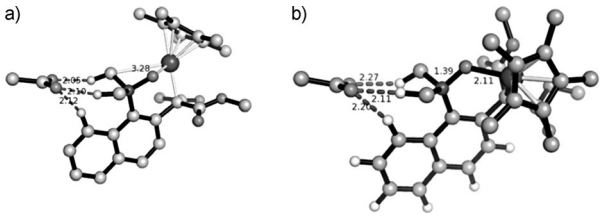
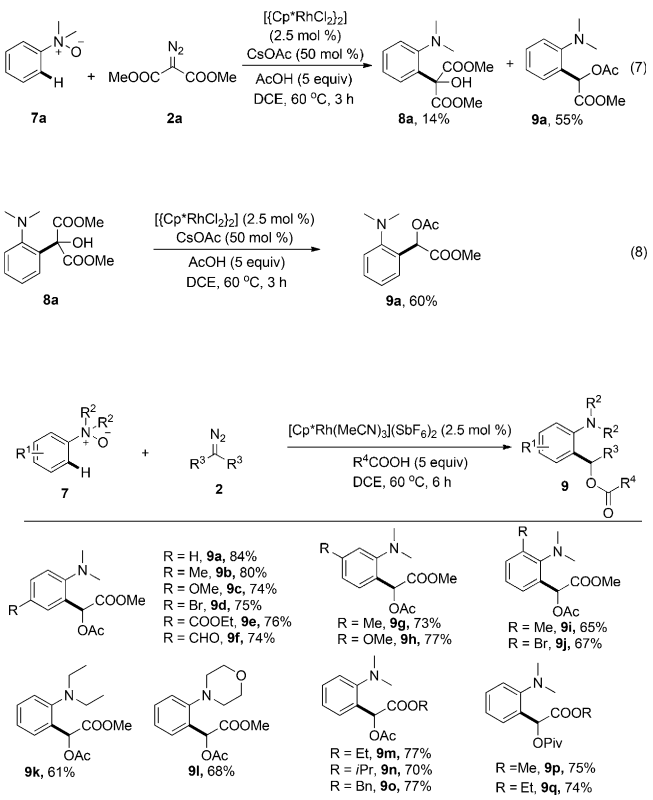


Figure 2. The stable complexes of **H** and acetate. a) The complex was optimized at M06/6-31G(d), via the complexes to TS1. b) The complex was optimized at M06/6-31+G(d), via the complexes to TS3.

this novel C(sp^3)–H cleavage. To further validate the importance of the C8–H bond, we treated *N*,*N*-dimethylaniline *N*-oxide (**7a**) with **2a** under the optimized reaction condition for 3 hours and no C(sp^3)–H cleavage was observed [Eq. (7)]. Instead the intermediate **H** underwent an oxygen-atom transfer reaction[18] to afford an aryl tertiary alcohol **8a** in 14% yield also with an aminomandelic acid derivative **9a** in 55% yield [Eq. (7)]. Satisfyingly, switching the [(Cp*$RhCl_2$)$_2$] catalyst to another well-known catalyst, [Cp*Rh(MeCN)$_3$](SbF$_6$)$_2$, gave **9a** (84% yield) as the sole product (also see Scheme 4). The compound **8a** could be converted into **9a** under the optimized rhodium(III)-catalyzed conditions, presumably by a cascade decarbonylation/hydroxy group elimination/nucleophilic addition, thus indicating the plausible intermediacy of **8a** in this reaction [Eq. (8)].

To further expand this coupling reaction, the scope of this methodology was subsequently explored (please see pages 2–4 in the Supporting Information for the detailed reaction



Scheme 4. Rhodium(III)-catalyzed coupling reaction of aniline *N*-oxides with α-diazomalonates. Reaction conditions: 0.2 mmol of **7**, 0.24 mmol of **2**, [Cp*Rh(MeCN)$_3$](SbF$_6$)$_2$ (2.5 mol%), R^{4}COOH (500 mol%), DCE (2 mL) at 60°C for 6 h. Yield of isolated product.

mechanism). As summarized in Scheme 4, various aniline *N*-oxides bearing electron-donating or electron-withdrawing groups on the phenyl ring were found to be effective substrates, thus affording **9b–j** in 67–84% yield. With the assistance of the *N*-oxide group, the C–H bond activation occurred exclusively at the *ortho* postion to provide *ortho*-functionalized tertiary anilines.[19] It is important to stress that the 3-Me (**9g**) and 3-OMe (**9h**) derivatives exhibited excellent regioselectivity with respect to the the C–H bond. Particularly, the 2-Me (**9i**) and 2-Br (**9j**) derivatives are also well-tolerated, thus showing high tolerance for steric hindrance. Moreover, the bromo (**9d** and **9j**), the ester (**9e**), and even the carboxaldehyde (**9f**) groups were compatible with this coupling reaction, thus enabling additional functionalization at these positions. In addition to *N*,*N*-dimethylaniline *N*-oxides, the sterically more hindered *N*,*N*-diethylaniline and cyclic amine *N*-oxide could also proceed smoothly in this transformation to give the corresponding products (**9k,l**) in satisfactory yields, thus emphasizing the generality of this method. Other α-diazomalonates coupled smoothly in good to high yields (**9m–o**). We were pleased to find that the *O*-pivaloyl aminomandelic acid derivatives **9p** and **9q** could be also obtained in high yields just simply by changing AcOH to PivOH.

In summary, we have developed an unprecedented rhodium(III)-catalyzed regioselective redox-neutral annulation reaction of 1-naphthylamine *N*-oxides with diazo com-

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pounds by dual cleavage of $C(sp^3)$–H/$C(sp^2)$–H bonds. This coupling reaction proceeds under mild reaction conditions and does not need external oxidants, and the only by-products are dinitrogen and water. DFT calculations support that an intermediate iminium is most likely involved in the catalytic cycle. In addition, a rhodium(III)-catalyzed coupling of readily available tertiary aniline *N*-oxides with α-diazomalonates was also developed under external oxidant-free conditions to access various aminomandelic acid derivatives by an O-atom-transfer strategy.

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