Memory of Chirality (MOC) in Intramolecular sp³ C–H Amination

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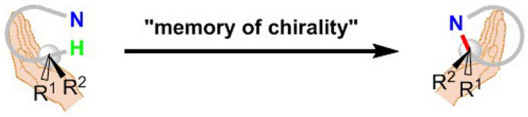

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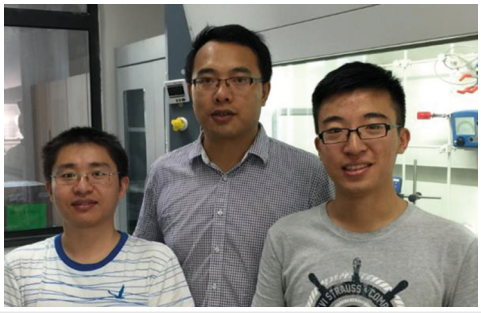
Abstract 'Memory of chirality' (MOC) is an important concept for the development of efficient asymmetric transformations. However, the phenomenon of MOC in C–H functionalization is still rare. In the past decades, three types of intramolecular C–H amination involving C–H insertion of metal nitrenoids, 1-aza-2-azoniaallene salts, and benzamides to construct N-heterocyclic compounds have been developed in Du Bois, Brewer, and our group, respectively. In these reactions, the formation of a C–N bond does not result in the loss of stereochemical information at the stereogenic center. Here, we discuss the scope, mechanism, and application of these transformations and provide a perspective on the development of this field in future.

Key words memory of chirality, asymmetric synthesis, N-heterocycles, amination, C–H functionalization

The concept of 'memory of chirality' (MOC) was proposed by Fuji in 1991, who successfully designed the enantioselective alkylation reactions at an asymmetric carbon adjacent to a carbonyl group.[1] This concept has been well defined by Matsumura as a process in which: '*the chirality of a starting material having a chiral sp³-carbon is preserved in the reaction product even though the reaction proceeds at the chiral carbon as a reaction center through reactive intermediates such as carbanion, singlet monoradicals, biradicals, or carbenium ions.*'[2] Later on, Carlier described the process of memory of chirality as follows: '*A 'memory of chirality' reaction can be defined as a formal substitution at an sp³ stereogenic center that proceeds stereospecifically, even though the reaction proceeds by trigonalization of that center, and despite the fact that no other permanently chiral elements are present in the system.*'[3] At the very beginning, the reaction type was still limited to few examples, including the alkylation of enolates,[1,4] and radical-trapping chemistry.[5] Recently, a wide range of 'memory-of-chirality' transformations in cross-couplings of classic electrophiles, such as benzylic halides, with Grignard, organozinc, and organoboron reagents have been developed in this context.[6]

With the development of C–H activation–functionalization strategies, the functionalization of unactivated sp³ C–H bonds under relatively mild reaction conditions is no longer

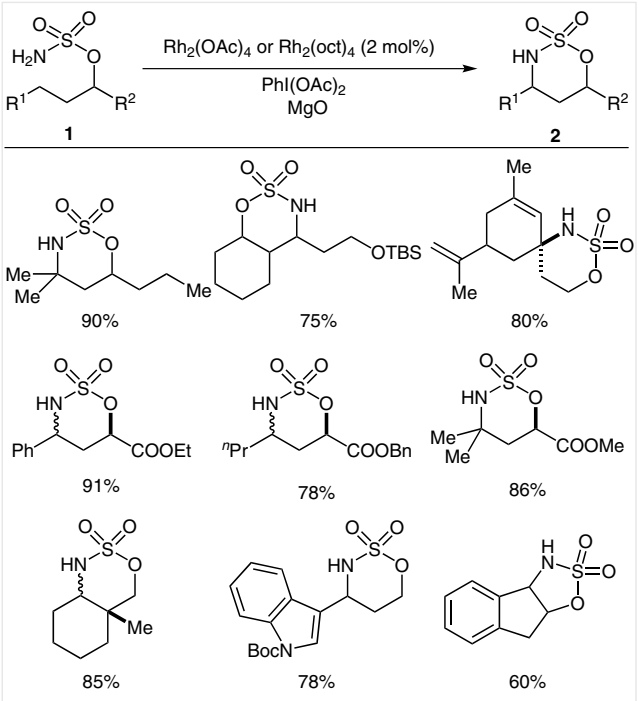


Chendan Zhu (left) obtained his BSc degree from the school of chemistry and chemical engineering of Jiangsu University in 2013. In the same year, he entered Nanjing University for further studies in chemical science. He now is a PhD candidate under the supervision of Prof. Shi. His research interest is synthetic methodology.
Zhuangzhi Shi (middle) was born in Jiangsu Province, P. R. of China. He received his BSc and MSc degree in chemistry and organic chemistry from Yangzhou University in 2005 and 2008. Then, he moved to Peking University and completed his PhD degree in medicine and organic chemistry with Prof. Ning Jiao. In 2011, he joined the group of Prof. Frank Glorius at Westfälische Wilhelms-Universität Münster as an Alexander von Humboldt Research Fellow studying rhodium(III)-catalyzed C–H activation reactions. Since March 2014, he is working as a full professor at the Nanjing University, focusing on the development of new transition-metal catalysts and synthetic methodology.
Yucheng Mu (right) was born in Jiangsu Province, P. R. of China, in 1994. He was admitted to Nanjing University as an undergraduate student in 2012 and enrolled in the Elite Undergraduate Program in Basic Sciences in 2013. In 2014, he joined Prof. Shi's research group to work on C–H functionalization reactions.

a major challenge in synthetic chemistry. Chemists put forward a new thinking: Can MOC take place in C–H functionalization reactions when the substrate has a stereogenic center with an sp^3 C–H bond? In order to achieve this goal, several challenges need to be surmounted regarding selective cleavage of the sp^3 C–H bond, because (1) a relatively high activation energy is required in the cleavage of an aliphatic C–H bond; (2) among various C–H bonds, the bond located at the stereogenic center needs to be activated selectively; and (3) the chiral information at the stereogenic center needs to be preserved during the transformation. Although a large number of sp^3 C–H functionalization reactions have been developed, the phenomenon of MOC in C–H functionalization is still rare.

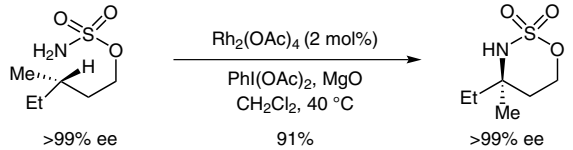
Intramolecular C–H amination has been the object of research for over 100 years, and a variety of well-established classical methods are now available.[7] The venerable Hofmann–Löffler–Freytag (HLF) reaction, discovered in the 1880s, remains one of the most powerful and versatile routes to the N-heterocycles, although this method suffers from several drawbacks.[8] A variety of synthetic modifications have been introduced in the past decades to increase the practicality and lessen the environmental impact.[9] Another efficient method is C,N-dianion oxidation including the process of tandem deprotonation of C–H and N–H bonds in the presence of strong bases (e.g., butyl lithium, Li sticks) and iodine reagents.[10] In the last few years, transition-metal-catalyzed C–H activation strategies have provided efficient routes to these heterocycles. Among them, the intramolecular C–H insertion of metal nitrenoids has been applied to the synthesis of highly complex alkaloids.[11] Recently, several groups have developed transition-metal-catalyzed aliphatic C–H amination–cyclization reactions utilizing different types of N-protected amides.[12] Among all these N-heterocycle-formation reactions mentioned above, memory of chirality is observed only in the C–H insertion of metal-nitrenoids. Most recently, Brewer and our group uncovered two N-heterocycle-construction methods involving C–H insertion of 1-aza-2-azoniaallene salts and benzamides, respectively. These novel transformations provide routes to stereospecific intramolecular sp^3 C–H amination and also expand the concept of MOC to new reaction types.

The standard method for generating the transient metal nitrenes is by metal-induced extrusion of nitrogen from azides. Che,[13] Dodd,[14] and Du Bois[15] discovered that metal-nitrenoid species could be prepared in situ from amine derivatives, iodine(III) reagents, and a transition-metal catalyst. Du Bois and co-workers reported examples of intramolecular sp^3 C–H amination using $PhI(OAc)_2$and MgO in the presence of a rhodium(II) carboxylate complex (Scheme 1).[16] These oxathiazinane products have exceptional value as precursors for 1,3-amino alcohols, β-amino acids, and numerous other 1,3-difunctionalized amine derivatives.



Scheme 1 Rhodium(II)-catalyzed intramolecular sp^3 C–H amination

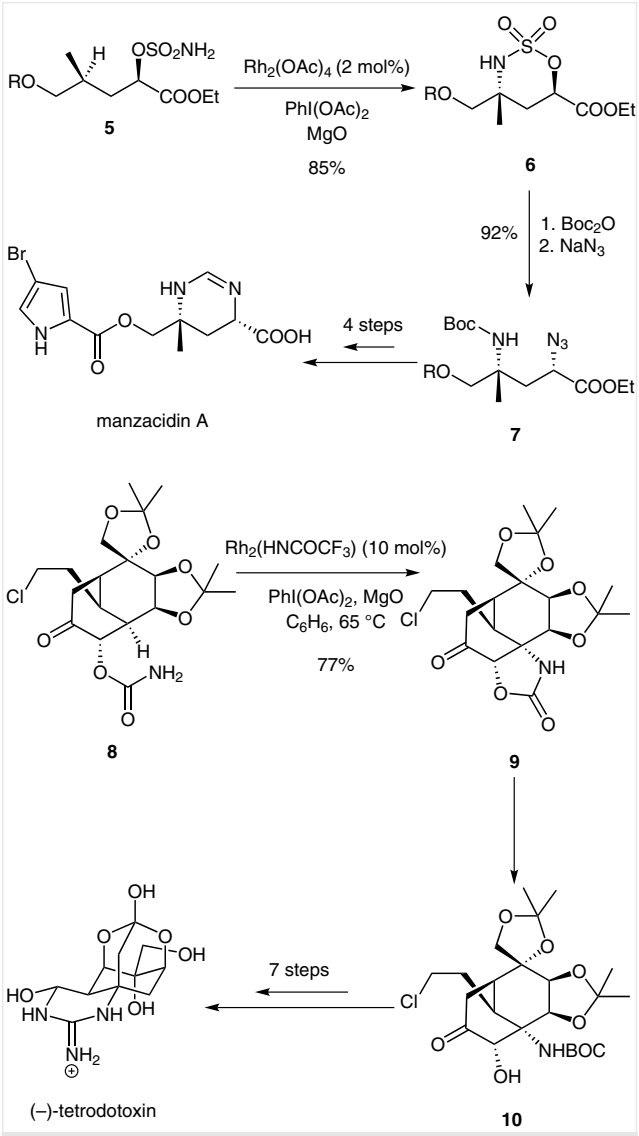
Remarkably, when substrate (*S*)-**3** was subjected to the standard conditions, oxathiazinane (*R*)-**4** was formed without erosion of enantiomeric excess (Scheme 2). This strategy shows the first case on MOC in C–H amination reaction in which C–N bond formation proceeds at the stereogenic sp^3 carbon as reaction center with retention.



Scheme 2 Memory of chirality in rhodium(II)-catalyzed intramolecular sp^3 C–H amination

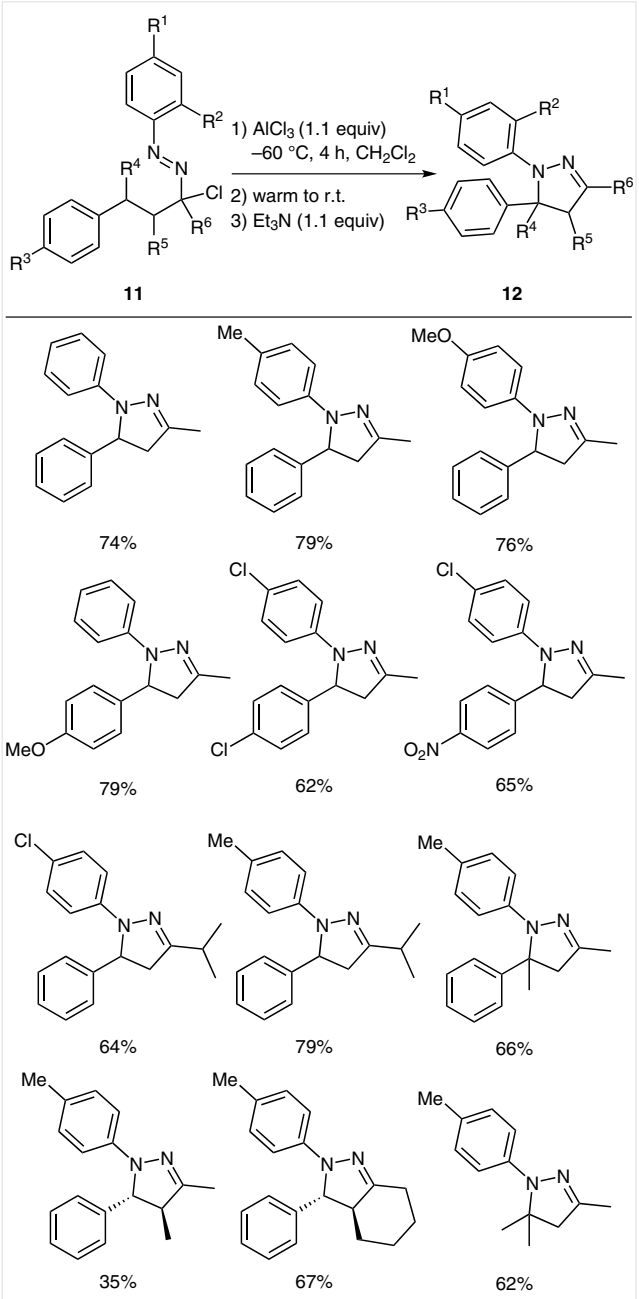
The stereospecificity of rhodium-catalyzed C–H aminations made the method a highly useful strategy to design natural products containing chiral N-heterocycles, which was later verified by several total syntheses published by the group of Bios (Scheme 3). The synthesis of the bromopyrrole alkaloid manzacidin A can serve as an example.[17] The pivotal intermediate **5**, prepared from ethyl glyoxylate in three steps, can be transformed into compound **6** by efficient oxidative cyclization with retention of configuration, followed by a S_N2-type ring-opening reaction and other subsequent four steps to afford the target. The stereospecific C–H amination, as the key process in the syn-

thesis, had a good yield of 85% and made the chirality of **6** match that of the natural product at the corresponding carbon atom. Another illustrative example was the total synthesis of (–)-tetrodotoxin.[18] The key intermediate **8** was decorated with dense functional groups by the previous 25 steps and the desired C–H amination proceeded in 77% yield. Also, at the same time, this step enabled the introduction of chirality at the specific carbon atom and was followed by seven steps to get the natural product.

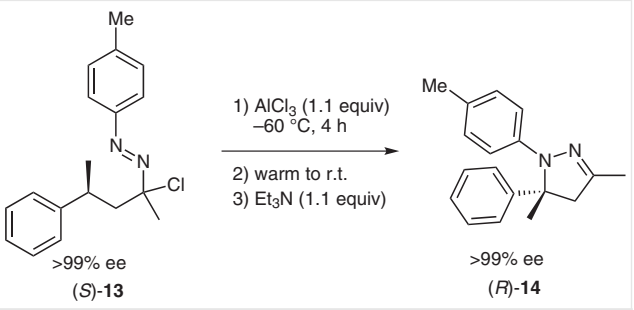


Scheme 3 Applications of intramolecular C–H amination in total synthesis

In 2012, the group of Brewer established a new strategy to synthesize N-heterocycles from aryl 1-aza-2-azoniaallene salts (Scheme 4).[19] These heteroallene species can be prepared directly from *N*-aryl hydrazones by oxidation or through the reaction of α-chloro azo compounds with halophilic Lewis acids such as $SbCl_5$ and $AlCl_3$. To test the scope of this reaction, they employed a series of substrates having either electron-donating or -withdrawing groups on the *N*-aryl or the pendant aryl ring. Furthermore, C–H amination could also take place at a tertiary nonbenzylic site. Interestingly, they also noticed that insertion at a chiral tertiary benzylic position occured with retention of stereochemical purity (Scheme 5). MOC did occur when using (*S*)-**13** as the starting material to afford the corresponding product (*R*)-**14** with complete stereochemical fidelity.



Scheme 4 Reaction development of C–H insertion of 1-aza-2-azoniaallene salt



Scheme 5 Memory of chirality in C–H insertion of 1-aza-2-azonia-allene salt

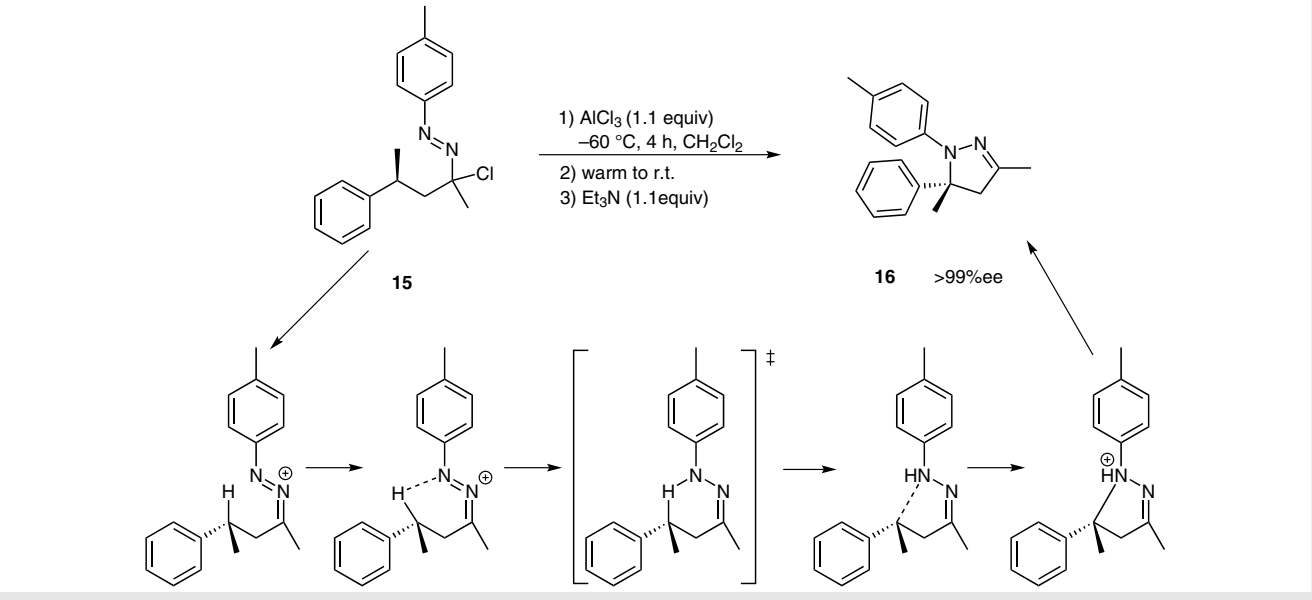
Very recently, the mechanism of C–H amination reactions of 1-aza-2-azoniaallene salts was studied experimentally and computationally in a collaborative project between the research groups of Brewer and Houk (Scheme 6).[20]

This transformation proceeds through a hydride-transfer transition state to form an N–H bond initially, and the subsequent C–N bond formation occurs spontaneously afterwards to generate the heterocyclic product. Intrinsic Reaction Coordinate trajectory indicates that the two consecutive bond-formation processes, N–H and C–N, are energetically concerted, and this concerted mechanism was further proved by quasi-classical molecular dynamics trajectory studies. The C–N bond formation occurred much faster than C–C bond rotation, which explained the stereospecificity in the C–H amination.

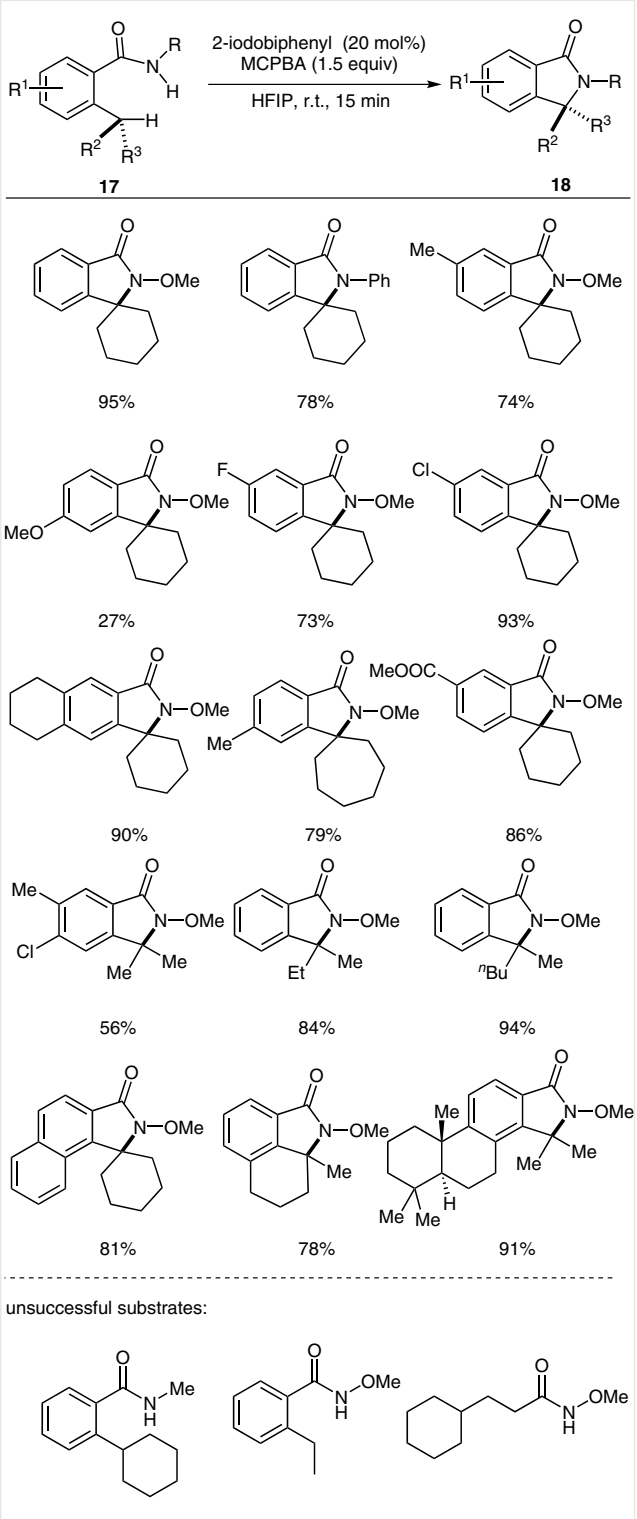
Research in hypervalent iodine chemistry has gained considerable momentum in recent years.[21] In particular, the emergence of catalytic processes with iodine(III) species is starting to make these competitive with metal catalysis. Kita and coworkers developed the first iodoarene-catalyzed C–N amination–cyclization process by dearomatization of arenes.[22] Antonchick's group also explored iodoarene-catalyzed or $PhI(OAc)_2$-mediated sp^2 C–N bond formation to construct the aza-heterocyclic skeletons including carbazoles,[23a] isoquinolones,[23b] and pyrido[1,2-*a*]benzimidazoles.[23c]

Recently, our group reported the first iodoarene-catalyzed intramolecular aliphatic C–H amination to synthesize γ-lactams.[24] Compared with the traditional methods requiring metal catalysts and complex functional groups in this transformation, our strategy utilized metal-free conditions and more available starting materials. We observed that using 2-iodobiphenyl as the catalyst, MCPBA as the oxidant and hexafluoro-2-propanol (HFIP) as the solvent, a series of γ-lactams can be easily accessed from various benzamides in 15 minutes (Scheme 7).

We found that the methoxy group on nitrogen atom can improve the reactivity of the cyclization. *N*-phenyl benzamide showed lower reactivity, and extending the reaction time to three days improved the yield to 78%. Electron-neutral and -deficient groups on the phenyl rings reacted well under the optimized conditions, but electron-rich substrate gave a poor yield due to side reactions. The reaction also worked well for naphthamide, and larger-scale transformation without notable erosion of yield proved the practicality of this new method. In addition, benzamide derived from (+)-totarol reacted smoothly and afforded the polycyclic lactam in excellent yield. Although this method could be complementary to some classical approaches, substrates containing substituents at the benzylic position and tertiary C–H bonds were the major limitation at current stage.

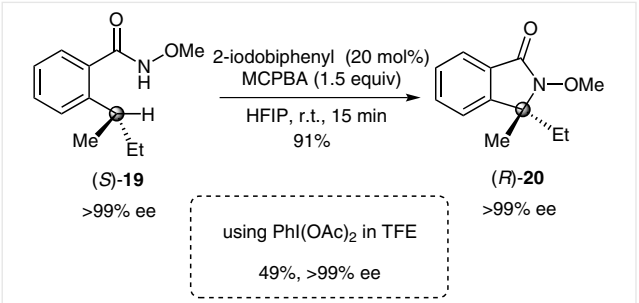


Scheme 6 Mechanistic insight into the C–H insertion of 1-aza-2-azoniaallene salt



Scheme 7 Reaction development of C–H insertion of benzamides

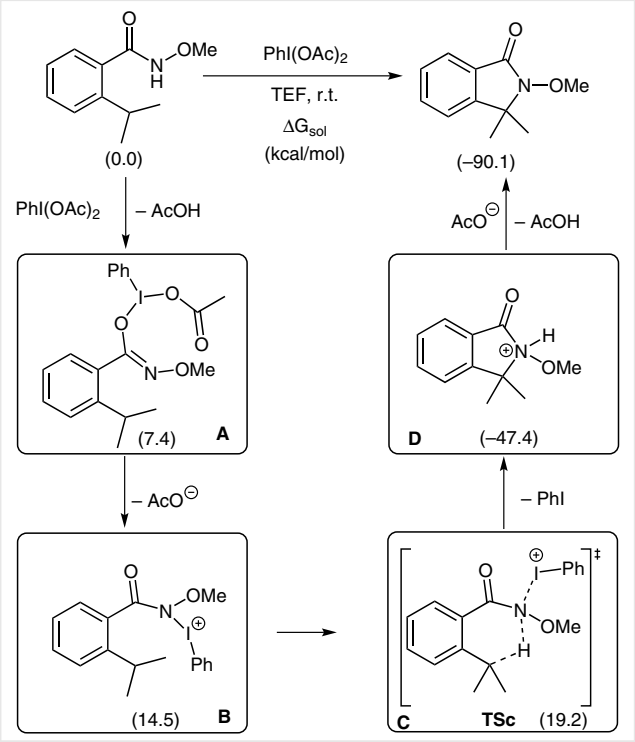
We next conducted an experiment with an enantioenriched substrate. Remarkably, when we subjected (*S*)-**19**-(*s*-butyl)-*N*-methoxybenzamide to the standard conditions, the (*R*)-**20**-ethyl-2-methoxy-3-methylisoindolin-1-one was formed in 91% yield without erosion of enantiomeric excess (Scheme 8). These stereospecific tertiary C–H aminations enabled the utility of this method in asymmetric synthesis. To better understand the mechanism of this sp^3 C–H amination, DFT calculations were performed by Houk and coworkers on this reaction. In order to simplify DFT calculations, we selected 2-isopropyl-*N*-methoxybenzamide as a model substrate, $PhI(OAc)_2$ as the oxidant, and TFE as solvent.



Scheme 8 Memory of chirality in C–H insertion of benzamides

As shown in Scheme 9, intermediate **A** is generated from the corresponding benzamide and $PhI(OAc)_2$ through ligand exchange on hypervalent iodine. This step is endergonic by 7.4 kcal/mol in TFE. From intermediate **A**, the electrophilic sp^3 C–H activation is evaluated, which can dissociate an acetate to generate an iodonium intermediate **B**, predicted to be endergonic by 7.1 kcal/mol in TFE. The iodonium cation **B** is predicted to be much more reactive toward nucleophilic sp^3 C–H activation. The hydride transfer from tertiary carbon to nitrogen via an S_N2-like transition state **TSc** requires an activation free energy of only 4.7 kcal/mol. This is in agreement with the recent discovery that the iodonium cation is the active intermediate in the iodine(III)-promoted C–C coupling. Based on the above calculation, this sp^3 C–H amination proceeds with MOC by an energetically concerted mechanism, where the hydride transfer is followed by the spontaneous C–N bond formation, akin to the well-known 'oxygen rebound' mechanism.[25] These stereospecific tertiary C–H aminations enable the utility of this method in total synthesis.

Memory of chirality is an emerging concept in the asymmetric synthesis and generally speaking, it includes the process of destruction of the original stereogenic center of the substrate, enantiospecific generation of a conformationally chiral intermediate, and subsequent transformation into a centrally chiral product. In this article, we highlight MOC applied to intramolecular sp^3 C–H amination involving C–H insertion of metal nitrenoids, 1-aza-2-



Scheme 9 Mechanistic insight of C–H insertion of benzamides

azoniaallene salts, and benzamides. These methods employ simple conditions to form the C–N bond and offer a possibility to form N-heterocycles in the total synthesis. Future work will be focused on the development of further MOC-type C–H functionalizations, and the related intermolecular reaction is also a big challenge for chemists.

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