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1,2,3-Triazoles as versatile directing group for selective sp^2 and sp^3 C–H activation: cyclization *vs* substitution†

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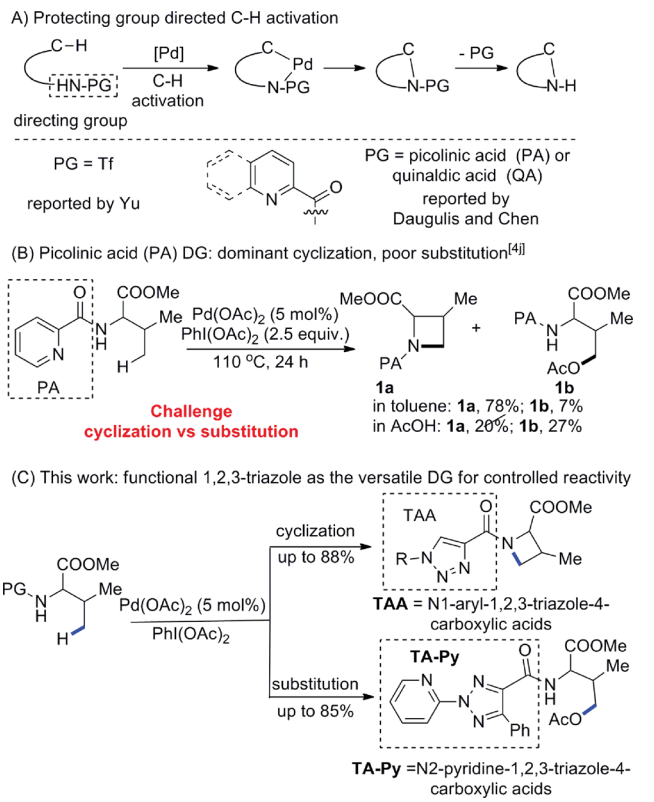
Selective cyclization and substitution was achieved with designated 1,2,3-triazole acid auxiliary groups under Pd catalyzed C–H activation conditions. Both sp^2 and sp^3 C–H bonds were effectively activated, giving the desired products in good yields. This result revealed the first successful example of exclusive substitution using 1,2,3-triazole ligands, while another triazole-containing directing group dominantly gave cyclization under identical conditions.

During the last decade, transition metal catalyzed C–H functionalization has been utilized as an efficient and versatile approach in complex molecule synthesis.[1] Among the reported methods, the directing group (DG) approach is particularly important since it can selectively activate specific C–H bonds.[2] Recently, Yu, Daugulis, and Chen groups reported the application of protected amides (HN-PG) as the directing group in Pd catalyzed C–H activation.[3–5] (Scheme 1A). This practical and conceptually novel strategy greatly enriches the reaction scope.

Although significant progresses have been achieved with this strategy, such as effective functionalization of sp^2 and sp^3 C–H bonds, one challenge is the chemoselectivity between cyclization and substitution. As shown in Scheme 1B, with the picolinic acid (PA) or quinaldic acid (QA) protecting groups, the cyclization products were dominant, even in the formation of highly strained azetidine rings. Recently, Chen and coworkers reported the application of alcohols as the co-solvents to promote the substitution over the cyclization.[4j] Although this work provided one successful example for O-substitution upon C–H activation using this auxiliary strategy, the requirement of an alcohol as a co-solvent limited the potential application for the incorporation of other functional groups due to the crucial competition from the alcohol solvent.[6] Thus, alternative versatile directing/protecting groups that render effective chemoselectivity control are highly desired. Herein, we report the first example of the application of 1,2,3-triazole-4-carboxylic acid derivatives as the alternative auxiliaries in adjusting the Pd catalyzed C–H activation (Scheme 1C). Effective sp^2 and sp^3 C–H activations can be successfully achieved and the desired cyclization and substitution products are prepared in good to excellent yields.

To be synthetically useful, the designed auxiliary group needs to be readily removable after C–H functionalization. As demonstrated in Scheme 2A, the 1,2,3-triazole 4-carboxylic acid can gave facile hydrolyzation under relatively mild conditions.[7] However, the 1,2,3-triazoles are highly electron-deficient



Scheme 1 Protecting/directing group promoted C–H activation.

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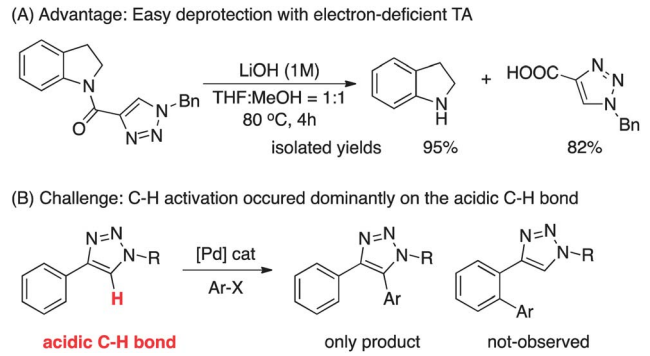


Scheme 2 Challenge in triazole-directed C–H activation.

aromatic compounds and therefore have been overlooked as potential ligands in transition metal coordination due to the assumed "poor" electron donating ability. In the last several years, our group has been working towards the development of new metal catalysts with 1,2,3-triazole ligands. Several stable triazole complexes were successfully prepared and characterized, revealing the good binding ability of 1,2,3-triazole towards transition metal cations, unlike the previous assumption.[8] Thus, we wondered whether 1,2,3-triazole-4-carboxylic acid derivatives (TAA) could be used as suitable auxiliaries in Pd catalyzed C–H activation.

One potential problem associated with our proposed strategy is the acidic C–H proton on 1,2,3-triazole.[9] Ackermann and coworkers have done comprehensive studies regarding the metal catalyzed C–H activation of conjugated triazole-phenyl compounds. Based on their results, under the Pd catalyzed conditions, C–H activation exclusively occurred on the triazole C–H bond (instead of the arene C–H, Scheme 2B).[10] Later, the same group reported Ru catalyzed C–H activation with 1,2,3-triazole directing group as part of the molecule.[11] So far, no Pd catalyzed triazole-directed C–H activation has ever been reported in the literature.

To test our hypothesis, triazole amide **2a** was prepared along with several other similar heteroaromatic amides. These substrates were screened under identical conditions, $(Pd(OAc)_2$ and $PhI(OAc)_2$ in DCE, 80 °C).

As shown in Fig. 1, the TAA directing group could effectively promote arene C–H activation, giving the cyclization product **3a** in 83% isolated yield, similar to quinaldic acid (QA) and

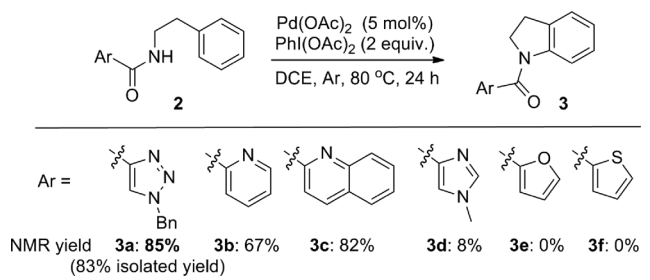


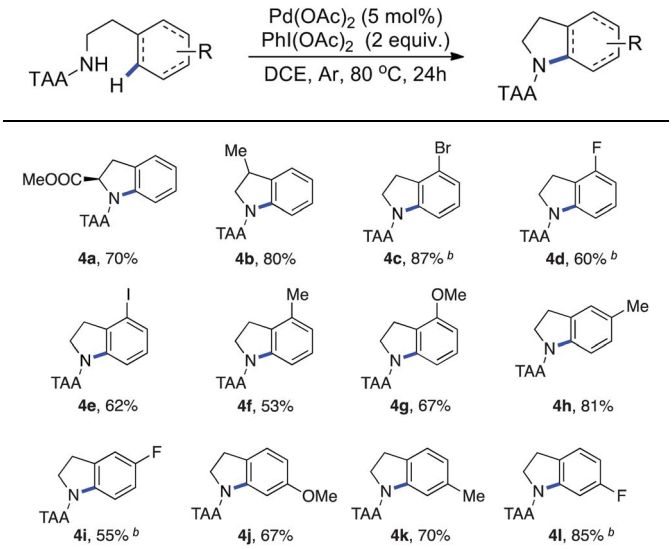
Fig. 1 TAA-directed C–H activation.

picolinic acid (PA) directing groups. To the best of our knowledge, this is the first example of 1,2,3-triazole directed arene C–H activation with Pd catalysts. Interestingly, other tested hetero aromatic compounds, such as imidazole, furan and pyrazole, could not promote this reaction at all, despite being more electron-rich than triazole. Various TAA derivatives were prepared to investigate the reaction scope.

As shown in Table 1, the triazole amide auxiliary effectively promoted the C–H activation sp^2 C–H bonds, furnishing the corresponding cyclization products in good to excellent yields. This transformation tolerated a large group of substrates. With the presence of both sp^2 and sp^3 C–H at the γ-positions, the reaction occurred exclusively on the sp^2 carbon (**4b**). Both EDG (**4g**, **4j**) and EWG (**4d**, **4i**, **4l**) substituted benzene were suitable for this reaction. Remarkably, with halides present on the *ortho* positions (**4c**–**4e**), the directed C–H activation occurred preferentially over oxidative addition, even for the aryl iodide (**4e**). Excellent regioselectivity was observed for the *meta*-substituted benzenes (**4h**, **4i**), giving the single cyclization products on the less sterically hindered *ortho*-carbon.

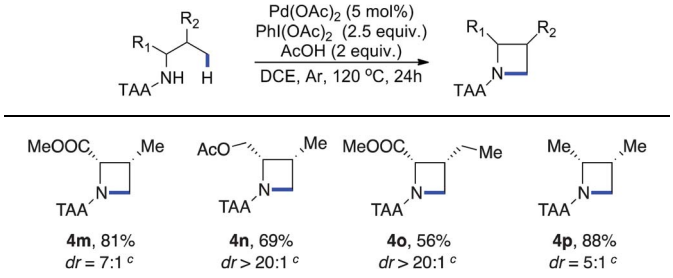
Similarly to PA-directed C–H activation, the reaction selectively occurred on the primary carbon (CH_3) over the secondary carbon (CH_2, **4o**) for the sp^3 C–H bonds (Table 2).[12] Formation of azetidines was observed in all cases, even with the presence of C–H at the δ-position (**4o**, for the synthesis of pyrrolidine). TAA amide from *tert*-octylamine were prepared and tested as a substrate that could undergo cyclization to form a pyrrolidine (CH_3 at the δ-position, formation of a 5-member ring). The cyclization product was observed with 84% isolated yield.[13] Good to excellent diastereoselectivity was observed. Notably, for both sp^2 and sp^3 substrates, cyclization products were the

Table 1 Reaction scope for TAA-directed sp^2 C–H activation[ac]



[a] The reactions were carried out with $Pd(OAc)_2$ (5 mol%) and $PhI(OAc)_2$ (2 equiv.) in 1,2-dichlorethane at 80 °C under Ar, unless otherwise mentioned. [b] Run at 100 °C. [c] Isolated yield.

Table 2 Reaction scope for TAA-directed sp^3 C–H activation[abd]

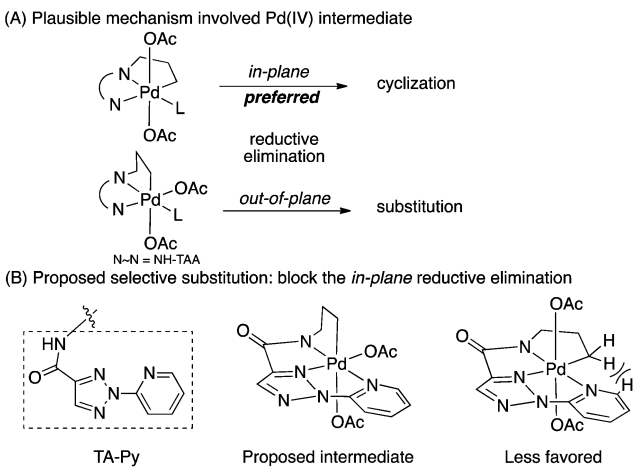


[a] The reactions were carried out with $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (2.5 equiv.), AcOH (2 equiv.) in 1,2-dichlorethane at 120 °C under Ar, unless otherwise mentioned. [b] TAA = N1-*p*-methyoxyphenyl-1,2,3-triazole-4-carboxylic acid. [c] Determined by ^1H NMR analysis. [d] Isolated yield.

dominant products observed with the TAA directing/protecting group.

Encouraged by the TAA-directed C–H activation, we then focused on the more challenging substitution reaction. PA, QA, and TAA directing groups all gave dominant cyclization products, which is consistent with a favored in-plane reductive elimination (Scheme 3A). We wondered whether the use of a tridentate directing group could force the Pd–C bond into the axial position (Scheme 3B), thereby favoring the out-of-plane C–O bond-forming reductive elimination pathway (Scheme 3A, bottom arrow).[14–16] The triazole-pyridine amide (TA-Py, **5a**) and pyridine-triazole acid (Py-TA, **5a′**) were prepared and charged with the standard oxidation conditions.

As shown in Fig. 2A, the tridentate Py-TA directing group **5a′** successfully blocked the cyclization reaction path. However, under the standard reaction conditions, no substitution product was obtained. Interestingly, when switching the protecting group from Py-TA to TA-Py, effective arene C–H activation was achieved and the substitution product **6a** was successfully obtained in 56% isolated yield (67% conversion,



Scheme 3 Proposed TA-Py directing group for selective substitution.

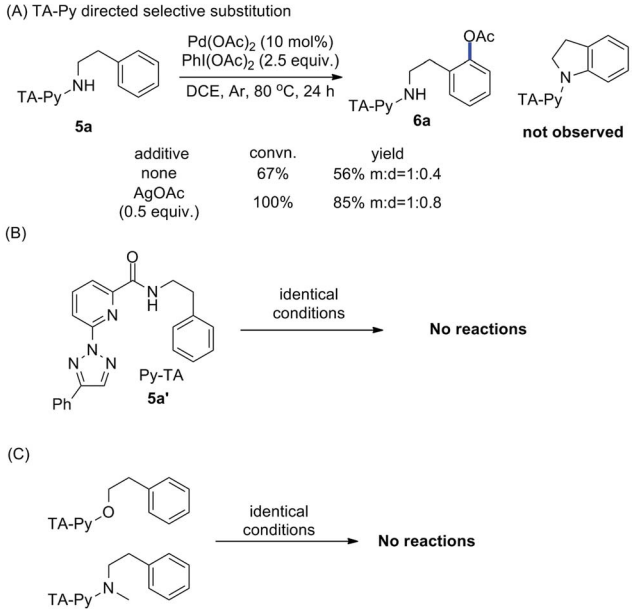
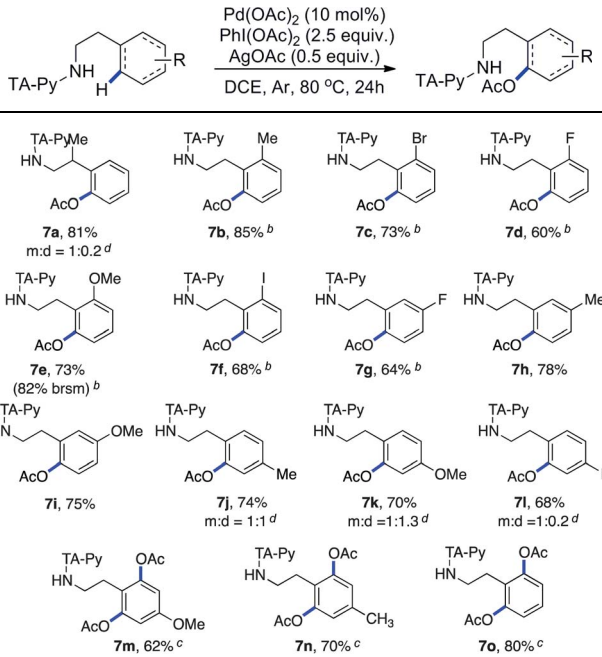


Fig. 2 TA-Py controlled selective substitution.

Fig. 2B). With the addition of AgOAc (0.5 equiv.) as the co-oxidant, the reaction achieved essentially 100% conversion, giving the substitution product **6a** (mixture of mono-OAc and di-OAc, m : d = 1 : 0.8) in excellent yields (85% isolated yields).[17] Notably, no cyclization product was observed under these conditions at all. To the best of our knowledge, the exclusive substitution (for the substrates that gave dominant cyclization reaction with PA, QA and TAA directing groups) revealed the first example of directing group controlled (over substrate controlled) selective C–H functionalization through designated protecting group tuning. Notably, both TA-Py ester and *N*-methyl TA-Py amide gave no reaction under identical reaction conditions (Fig. 2C). These results clearly indicated the required binding of amide nitrogen as the X-type ligand for the substitution reaction. Although it remains uncertain whether the reaction proceeds through the tridentate coordination mode at this moment, the successful substitution over cyclization provides a new strategy in achieving chemoselective C–H activation through simple directing group control.

Various TA-Py amides were prepared to evaluate the reaction scope. The results are summarized in Table 3. Similar to TAA, the TA-Py directing group could effectively promote the Pd catalyzed C–H activation for both sp^3 and sp^2 C–H bonds. A wide substrate scope was observed with this TA-Py protecting group. For sp^2-substrates, reactions occurred selectively on the *ortho*-C–H over the *ortho*-halides, including aryl iodide (**7c**, **7d**, **7f**). Both EDG (**7e**) and EWG (**7d**) modified arenes were suitable under the reaction conditions. Typically, mixtures of mono and di-acetoxylation products were observed when both *ortho*-C–Hs were present. Good yields were obtained for di-substitution in the present of excess oxidants (**7m**–**7o**). Excellent regioselectivity was received with the *meta*-substituted benzene, with substitution occurring at the less hindered carbons (**7g**–**7i**).

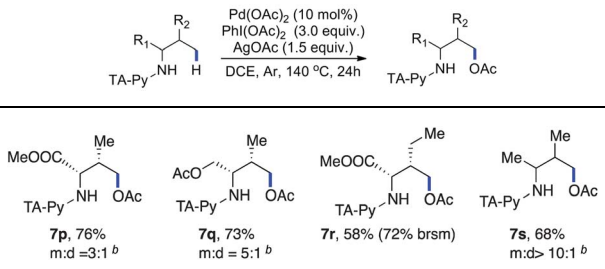
Table 3 Reaction scope for TA-Py directed sp^2 C–H activation[ae]



[a] The reactions were carried out with $Pd(OAc)_2$ (10 mol%), AgOAc (0.5 equiv.) and $PhI(OAc)_2$ (2.5 equiv.) in 1,2-dichloroethane at 80 °C under Ar, unless otherwise mentioned. [b] Run at 100 °C. [c] $PhI(OAc)_2$ (3 equiv.) was used at 100 °C. [d] The ratio of the mono-substitution to di-substitution was determined by ^{1}H NMR analysis. [e] Isolated yield.

The reaction also worked well with sp^3 C–H substrates, giving the desired substitution products in good isolated yields (Table 4). Notably, all these substrates gave the dominant cyclization products with PA, QA and TAA directing groups while the TA-Py directing group gave no cyclization products in all cases. Similar to TAA, the TA-Py selectively directed the C–H activation at the primary carbon (CH_3) over the secondary carbon (CH_2, **7r**). The reaction also gave very good diastereoselectivity as shown in **7p–7r**. The stereogenic centers in the starting materials did not epimerize under the reaction conditions, which suggests potential applications of this strategy in complex molecule synthesis.

Table 4 Reaction scope for TA-Py-directed sp^3 C–H activation[ac]



[a] The reactions were carried out with $Pd(OAc)_2$ (10 mol%), AgOAc (1.5 equiv.) and $PhI(OAc)_2$ (3.0 equiv.) in 1,2-dichloroethane at 140 °C under Ar, unless otherwise mentioned. [b] The ratio of the mono-substitution to di-substitution was determined by ^{1}H NMR analysis. [c] Isolated yield.

Conclusions

In conclusion, we have developed a directing/protecting group controlled selective substitution or cyclization with designated 1,2,3-triazole directing/protecting groups in the Pd catalyzed sp^2 and sp^3 C–H activation. This work provided the first example of Pd catalyzed C–H activation with the 1,2,3-triazole directing group. The success in the challenging substitution with the TA-Py directing group provided the opportunity for other C–H functionalization through the Pd catalyzed C–H activation by overcoming the inherent cyclization pathway. In addition, the sequence dependent directing group effect (TA-Py over Py-TA) further emphasized the unique reactivity of 1,2,3-triazoles as ligands in Pd catalyzed reactions, which will open the door for further developments.

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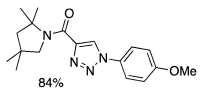
13 Five member ring cyclization (formation of pyrrolidine) can also be achieved in good yield with the TAA directing group.



84%

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17 See ESI† for detailed condition screening for Pd-catalyzed acetoxylation.