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1,2,3-Triazole amine as directing group in promoting catalytic oxidative C–H olefination under aerobic conditions

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ABSTRACT

A practical *ortho* C–H olefination of phenyl acetic acid derivatives was achieved with a 1,2,3-triazole auxiliary directing group. Good to excellent yields were achieved with O_2 as terminal oxidant. Other bidentate directing groups, such as 8-aminoquinoline, gave poor reactivity under this aerobic condition, highlighting the unique reactivity of triazole in promoting C–H activation.

1. Introduction

During the past decade, transition metal catalyzed C–H activation has been widely applied as an efficient approach in complex molecule synthesis.[1] Pd-mediated C–H oxidative olefination, known as the Fujiwara–Moritani oxidative Heck reaction, is one of the most important transformations for arene functionalization.[2,3] However, this transformation generally suffers from poor selectivity (relying on the different C–H bond reactivity).[4] The directing group strategy provides an alternative approach to overcome this issue by offering highly selective functionalization at the *ortho* C–H position. So far, several directing groups (DGs) have been reported in promoting the C–H olefination, including OR, COOH and pyridine.[5] Although excellent selectivity was achieved, most of the reported directing groups suffered one major drawback: the use of stoichiometric amounts of expensive oxidant (such as AgOAc, Selectfluor, etc.) were required. Thus, our interests were triggered to develop a new directing group system, which allows this transformation under aerobic conditions (Fig. 1).

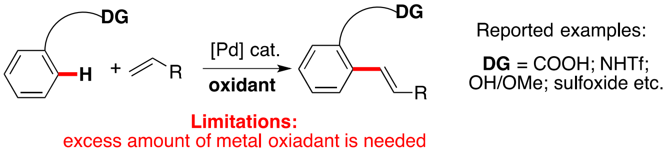

Fig. 1. Selective C–H olefination using directing groups.

Besides the requirement of strong oxidant, another limitation of directing group strategy was that the DG has to be part of the substrate. Thus, to enhance this powerful directing C–H activation strategy, removable bidentate-auxiliary directing groups have been developed. According to literature, pyridine and quinoline modified protecting groups are the most popular heterocycles in facilitating this type of transformation.[6] Recently, our group reported the 1,2,3-triazole-4-carboxylic acid as another versatile removable directing group (formation of triazole amide) in promoting selective C–H olefination.[7] This new triazole directing group not only gives the desired products in excellent yields (up to 95%), but also allows molecular oxygen (1 atm O_2) to be used as terminal oxidant,

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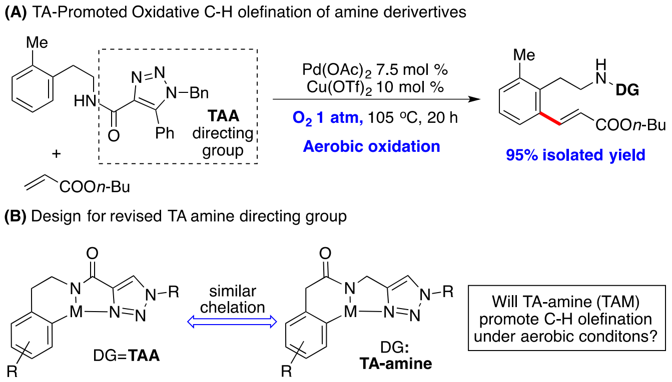
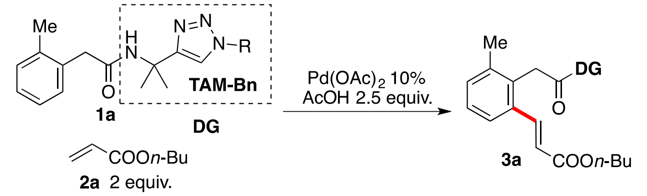


Fig. 2. Triazole group directed C–H activation.

emphasizing the high efficiency of triazole DG in promoting inactive C–H functionalization (Fig. 2A).

2. Results and discussion

In 2014, the Ackermann group introduced a novel TA-amine directing group using easily accessible 1,2,3-triazole for iron catalyzed C–H activation.[8] Encouraged by the result that TA amide could successfully promote the C–H olefination under aerobic conditions, we postulate that revised TA-amine may be a suitable directing group to promote the acid directed C–H olefination under aerobic condition without using any expensive external oxidant (Fig. 2B).[9] To verify this idea, several triazole-amine modified substrates were prepared and reacted with alkene **2a** under standard oxidation conditions. The results are summarized in Fig. 3.



Additional conditions	convn. (%)	yield of **3a** (%)
$Cu(OTf)_2$ 10%; O_2 1 atm, 105 °C, 12 h	50%	45%
$Cu(OTf)_2$ 20%; O_2 1 atm, 105 °C,12 h	<10%	<10%
no $Cu(OTf)_2$; O_2 1 atm, 105 °C, 12 h	95%	85%
DG=TAM-Ph (R=Ph) 2 equiv. butyl acrylate, 7.5% $Pd(OAc)_2$ O_2 1 atm, 80 °C, 12 h	100%	95%

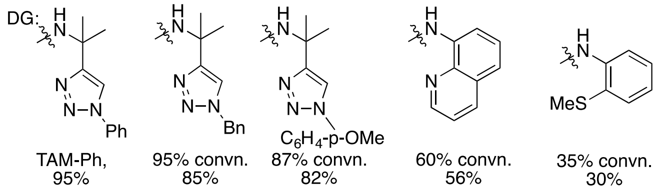


Fig. 3. Triazole-amine directed aerobic C–H olefination.

First, using previously optimized conditions with triazole acid directing group, 10% $Pd(OAc)_2$, 10% $Cu(OTf)_2$, 2.5 equiv HOAc in 1,4-dioxane with 1 atm O_2, the desired C–H olefination product **3a** was formed with the triazole-amine directing group, though with much lower yield (45%, 50% conversion of **1a**). Interestingly, increasing the amount of $Cu(OTf)_2$, which proved to be an effective additive for previous cases, shut down the overall reaction with only trace product **3a** obtained.[10] We postulated that it might be due to a stronger coordination of cooper metal towards triazole amine (unlike triazole acid), which inhibit the Pd coordination/C–H activation. In fact, without copper salt as additive, the reaction achieved 95% conversion and 85% yield. Alternatively, tuning the electron properties by switching benzyl group on N1 position to phenyl lead to the complete conversion of **1a** with 95% isolated yield of olefination product **3a**, even at lower temperature (80 °C).[11] Notably, triazole C–H olefination was not observed, which highlighted the mild conditions in this aerobic oxidation condition.[12]

To compare and evaluate the reactivity of the triazole amine directing group, substrates containing other common directing groups were prepared and evaluated under the same conditions. As shown in Fig. 3, N1 phenyl substitution was identified to be the optimal DG with balanced electronic effect in promoting this transformation.[13] Notably, 8-aminoquinoline and 2-aminophenylthio ether, which have been used in the olefination with strong oxidant, gave poor results under the aerobic oxidation conditions.[14] These results highlighted the unique reactivity of 1,2,3-triazole directing groups in promoting C–H activation.

As shown in Fig. 4, the TAM-directing group tolerated a large number of substrates, furnishing the corresponding olefination in good to excellent yields. Both EDG (**3a**) and EWG (**3c**, **d**) modified arenes were suitable for this reaction. Although substitution occurs primarily at the less hindered *ortho*-carbons position (**3e**–**3f**) for *meta*-substituted benzene ring, the di-olefination was also observed. Typically, the selectivity of mono and di-olefination would be poor when both *ortho*-C–Hs were present (**3g**–**3i**). This problem was overcomed through increasing the steric bulkiness at the benzylic position. As shown in **3j**, incorporation of a methyl group effectively improved the mono:di selectivity to >20:1. Meanwhile, using excess amount of alkene (4 equiv) gave the di-olefination in good yields (**3m**–**3o**). However, benzoic acid derivatives are proved to be ineffective under this condition as one limitation for this transformation.

The scope of alkene was also evaluated. Besides acrylate, most of other activated alkenes, such as, vinyl phosphate (**5d**), vinyl sulfone (**5e**) are suitable for this transformation, giving the desired olefins in excellent yields. Impressively, non-active olefins, such as styrene derivatives, could also undergo this transformation with good to excellent yields (**5f**–**5g**). Moreover, the coupling with estrone derivatives was also successfully achieved, showing the potential application of this method. However, similar to other reported oxidative Heck-type reactions, α, β substituted alkenes failed to give the desired products due to steric hindrance on either alkene insertion or β-hydride elimination steps. Nevertheless, the broad substrate scope, simple reaction conditions and use of atmosphere oxygen as the oxidant highlighted the advantages of this new triazole-directing group in promoting selective C–H olefination.

3. Conclusion

In conclusion, we have unveiled 1,2,3-triazole as an effective directing group in promoting aerobic C–H oxidative olefination. This study not only revealed a new efficient and economic approach (using 1 atm O_2 as the terminal oxidant) in achieving selective C–H olefination, but also confirmed the versatile reactivity of 1,2,3-