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Synthesis of 3-pyrroline via domino Heck–aza-Michael reaction

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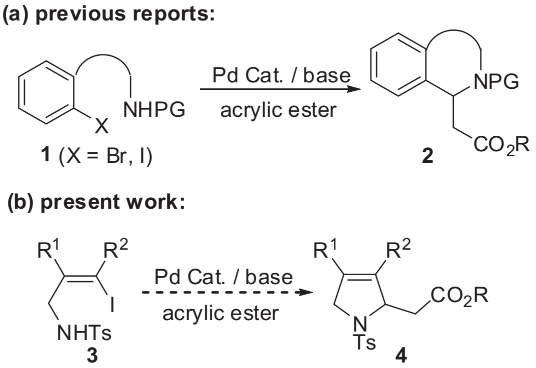
ABSTRACT

This Letter describes the Pd(0)-catalyzed domino Heck–aza-Michael reaction between (*Z*)-*N*-(3-iodoallyl)-tosylamide and acrylic ester. The reaction provides a facile access to an important class of substituted 3-pyrroline.

Domino reactions, where a series of reactions proceed in a defined order in one sequence, have emerged as a powerful tool for organic synthesis due to their well-known advantages, such as economies of time, labor, and resource management, as well as efficient construction of complex molecules.[1] In recent years, the strategy of couple metal-catalysis and classical reactions in a single one-pot operation to achieve domino sequence has been realized.[2] In this context, the palladium-catalyzed Heck-reaction of acrylic ester is an ideal platform because of the following facts: (1) acrylic esters are commercial chemicals; (2) they are able to undergo facile Heck-reaction; (3) most importantly, the newly formed α,β-unsaturated esters are readily available for Michael addition, especially intramolecular variant. Indeed, a domino process combining Heck and aza-Michael reactions has been developed with the use of **1** and acrylic ester as substrates (Scheme 1a).[3] This process provides a facile entry to various benzo-azaheterocycles **2**.

As our continuous efforts on the palladium-catalyzed transformation of (Z)-vinyl iodide,[4] we are interested in compounds **3** due to its similar reactivity with that of **1** with respect to the domino Heck and aza-Michael process (Scheme 1b). Furthermore, compounds **3** can be readily synthesized in gram scale with a simple two-step procedure.[5] Herein, we report a domino Heck and aza-Michael reaction between **3** and acrylic ester (Scheme 1b). This new reaction complements the previous cases of substrate **1**, as far as it allows access to a range of 3-pyrrolines **4**, whose olefin and ester groups are capable of further transformations to synthesize complex molecule.

When a mixture of **3a** (1 equiv) and *tert*-butyl acrylate **5a** (2.5 equiv) was treated with $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), and Na_2CO_3 (2 equiv) in refluxing THF for 14 h, it was pleased to find that the desired product **4aa** could be isolated albeit only in 10% yield (Table 1, entry 1). Solvent screening disclosed that dioxane is the optimal one, enabling **4aa** being isolated in 48% yield (Table 1, entries 2–6). To our delight, Bu_4NBr (2 equiv) was found to be an efficient additive,[6] increasing the yield to 65% (Table 1, entry 7). However, we could not improve the yield of **4aa** any more, although other reaction parameters, including ligand and base, were thoroughly investigated (Table 1, entries 8–13). It should be noted that the use of 2.5 equiv **5a** is mandatory for higher yield. Indeed, the use of 2.0 equiv **5a** led to 55% yield



Scheme 1. Domino Heck and aza-Michael reactions.

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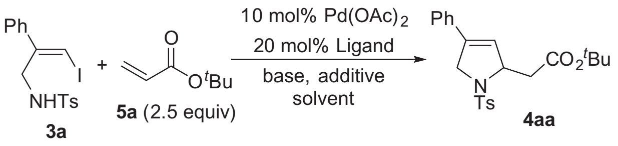
Table 1
Reaction conditions optimization[a]



Entry	Ligand	Base (2 equiv)	Solvent	Additive (2 equiv)	Isolated yield (%)
1	PPh_3	Na_2CO_3	THF[b]	–	10
2	PPh_3	Na_2CO_3	MeCN[b]	–	42
3	PPh_3	Na_2CO_3	PhMe[c]	–	11
4	PPh_3	Na_2CO_3	DMF[c]	–	13
5	PPh_3	Na_2CO_3	DMSO[c]	–	<5
6	PPh_3	Na_2CO_3	Dioxane[c]	–	48
7	PPh_3	Na_2CO_3	Dioxane	Bu_4NBr	65
8	$(4\text{-}FC_6H_4)_3P$	Na_2CO_3	Dioxane	Bu_4NBr	44
9	$(2\text{-Furan})_3P$	Na_2CO_3	Dioxane	Bu_4NBr	30
10	PPh_3	K_2CO_3	Dioxane	Bu_4NBr	36
11	PPh_3	Ag_2CO_3	Dioxane	Bu_4NBr	9
12	PPh_3	DBU	Dioxane	Bu_4NBr	<5
13	PPh_3	Et_3N	Dioxane	Bu_4NBr	<5
14[d]	PPh_3	Na_2CO_3	Dioxane	Bu_4NBr	55
15[e]	PPh_3	Na_2CO_3	Dioxane	Bu_4NBr	63

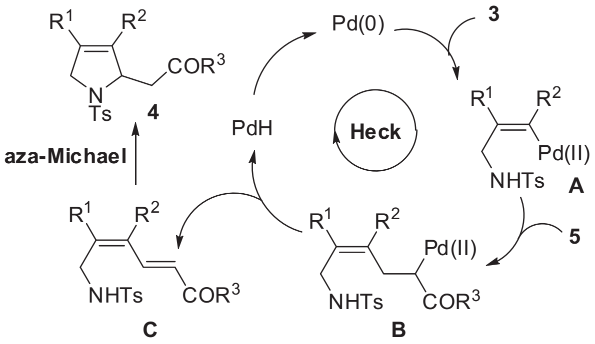
[a] Reaction conditions see Supplementary data.

[b] Refluxing.

[c] 100 °C.

[d] 2.0 equiv of **5a** was used.

[e] 3.0 equiv of **5a** was used.



Scheme 2. The proposed mechanism.

of **4aa** (Table 1, entry 14) while 3.0 equiv **5a** was found not to be any positive effect (Table 1, entry 15).

With the optimized reaction conditions in hand, we then turned our attention to investigate the reaction scope and the results are summarized in Table 2. Firstly, various substrates **3** were tested. Both alkyl and aryl substituents at C2-position of **3** are well tolerated (Table 2, entries 1 and 2). But the reaction of substrate **3c** with a butyl group at C1-position gave no corresponding product while **3c** was recovered in 89% yield (Table 2, entry 3). This failure might stem from less reactivity imposed by steric hindrance of butyl group. However, substrates with phenyl substituted at C1-position, such as **3d** and **3e**, show good reactivity, delivering the corresponding products with good yields (Table 2, entries 4 and 5). Secondly, a range of substrates **5** were also investigated. Likely due to its high volatility, the reaction of methyl acrylate **5b** affords **4ab** in somewhat lower yield. The yield of **4ab** can be improved to be 71% when 5.0 equiv **5b** is used instead (Table 2, entry 6). Somewhat surprisingly, the reaction of α,β-unsaturated ketone **5c** with **3a** gave **4ac** only in 43% yield (Table 2, entry 7). It was pleased to find that the reaction protocol was also applicable to acrylamide. Indeed, substrates **5d** and **5e** reacted well with **3a**, delivering **4ad** and **4ae** in 43% and 40% yields, respectively (Table 2, entries 8–9).

On the basis of previous reports[3] and the present results, we proposed a possible mechanism of this transformation (Scheme 2). This would involve the oxidative addition of vinyl iodide **3** to Pd(0) center to initiate Heck-type reaction with acrylic ester, which leads to the formation of intermediate **C**. Subsequently, aza-Michael addition occurs to afford pyrroline product. It should be mentioned that intermediate **C** could not be detected in the course of reaction, indicating that the subsequent aza-Michael addition might be a fast step.

The products of the present Heck–aza-Michael reaction can be converted into other potentially useful compounds (Scheme 3). For example, the ester group of **4aa** can be readily hydrolyzed to afford acid **6**, which underwent iodolactonization[7] to give compound **8** as a single diastereomer in the presence of I_2 and $NaHCO_3$. With the treatment of $LiAlH_4$, **4aa** can be reduced to afford alcohol **7**. Similarly, after bromoetheration in the presence of NBS,[8] **7** can be converted into bridged compound **9**.[9]

In summary, we have developed a Pd(0)-catalyzed Heck–aza-Michael domino reaction of (Z)-3-iodoprop-2-en-1-amine derivative with acrylic ester, which complements the related reactions of 2-iodoaniline. It provides a convenient access to a variety of substituted 3-pyrrolines in mediate to good yields. Further expansion of the reaction scope and synthetic applications are underway.

Acknowledgments

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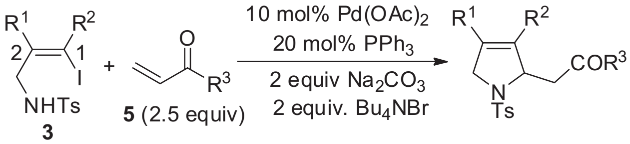
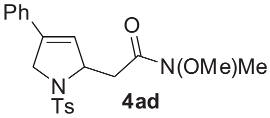
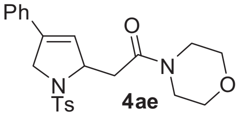
Table 2
Reaction scope[a]

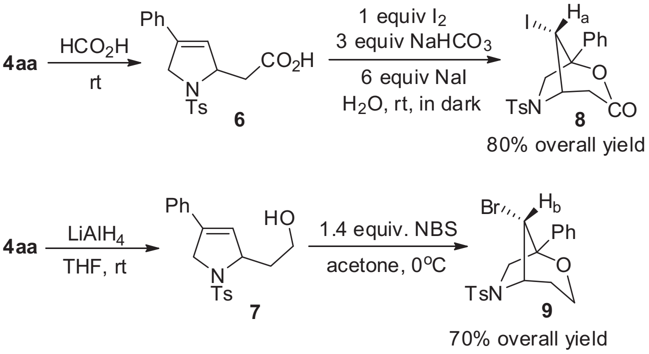


Entry	**3** (R^1, R^2)	**5** (R^3)	**4**	Yield[b] (%)
1	**3a** (Ph, H)	**5a** (O^{t}BU)	**4aa**	65
2	**3b** (Bu, H)	**5a** (O^{t}BU)	**4ba**	50
3	**3c** (Et, Bu)	**5a** (O^{t}BU)	**4ca**	ND
4	**3d** (Ph, Ph)	**5a** (O^{t}BU)	**4da**	51
5	**3e** (Et, Ph)	**5a** (O^{t}BU)	**4ea**	70
6	**3a** (Ph, H)	**5b** (OMe)	**4ab**	54 (71)[c]
7	**3a** (Ph, H)	**5c** (Ph)	**4ac**	43
8	 **4ad**			43
9	 **4ae**			40

[a] Reaction conditions see Supplementary data.

[b] Isolated yield.

[c] The data in parentheses was obtained with the use of 5.0 equiv **5b**.



Scheme 3. Synthetic transformation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.075.

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