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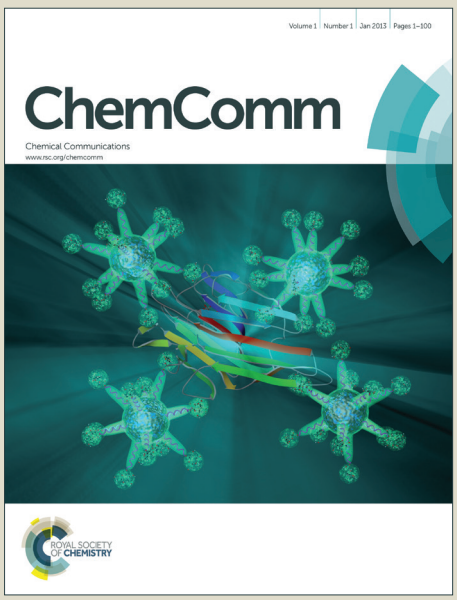

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ARTICLE TYPE

Direct access to isoindolines through tandem Rh(III)-catalyzed alkenylation and cyclization of *N*-benzyltriflamides

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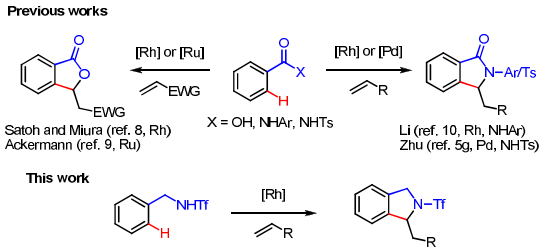
The rhodium-catalyzed oxidative alkenylation of *N*-benzyltriflamides with olefins followed by an intramolecular cyclization via C–H bond activation is described. This method results in the direct and efficient synthesis of highly substituted isoindoline frameworks.

The Isoindoline heterocycles have demonstrated potential in organic and medicinal chemistry as they exhibit diverse biological activities and interesting chemical properties. For example, the isoindoline motif is present in molecules that act as selective PPARδ agonists, molecular chaperone Hsp90 inhibitors, endothelin-A receptor antagonists, and dipeptidyl peptidases inhibitors.[1] Moreover, isoindoline derivatives are very crucial constituents in the field of material science as attractive candidates for organic light-emitting devices.[2] Therefore, the development of novel and highly efficient strategies for the formation of these heterocyclic architectures is an area of great interest in organic synthesis. Transition-metal-catalyzed C–H bond activation has emerged as an atom economical process to produce structurally diverse organic molecules due to the minimization of stoichiometric metallic waste. Thus, the cross-coupling reactions via C–H bond activation can lead to an improved overall efficiency of the desired transformation.[3] Since the pioneering efforts of Fujiwara and Moritani,[4] remarkable progress has been made on the oxidative olefination of arenes using alkenes under palladium catalysis to directly functionalize arene C–H bonds.[5] In contrast to the vast majority of reports on the palladium-catalyzed olefinations, the oxidative C–H olefinations using rhodium catalysts, which often allow lower catalytic loadings, higher selectivities, and broad substrate scope, have been much less explored.[6] For instance, Matsumoto and Yoshida described an oxidative coupling reaction between benzenes and ethylene using cyclometalated Rh(III) catalysts to afford styrenes.[7] Notably, Satoh and Miura[8] and Ackermann[9] respectively reported Rh(III)- and Ru(II)-catalyzed oxidative coupling and intramolecular cyclization between benzoic acids and acrylates. Li disclosed Rh(III)-catalyzed tandem oxidative olefination and aza-Michael reaction of secondary benzamides with α,β-unsaturated alkenes (Scheme 1).[10] In addition, a great deal of effort has been devoted to the selective olefination of arenes with various directing groups such as pyridinyl,[11] hydroxyl,[12] esters,[13] anilides,[14] carbamates,[15] and ketones/amides.[16] A triflamide moiety as a directing group was first introduced by Yu for the palladium-catalyzed C–H bond functionalization, and can be transformed to a range of synthetically useful functional groups.[17] Our continued efforts in rhodium- or palladium-catalyzed C–H bond activation and oxidative acylation reactions[18] prompted us to explore the coupling reaction of *N*-benzyltriflamides with olefins.



Scheme 1 Catalytic oxidative olefination and cyclization protocols.

In our initial study, *N*-(2-methoxybenzyl)triflamide (**1a**) and *n*-butyl acrylate (**2a**) were chosen as model substrates for optimizing the reaction conditions (see Supplementary Information for optimization table). After extensive screening of amine protection groups such as Ac, Bz, Piv, Ts, $COCF_3$ and SO_2CF_3 (Tf), benzylamine **1a** with triflamide directing group was found to couple with 150 mol % of acrylate **2a** in the presence of 10 mol % of $Pd(OAc)_2$ and 200 mol % of $Cu(OAc)_2$ in DCE solvent at 110 °C for 24 h to give the alkenylation compound **3aa** in 27% yield. After screening of solvents under palladium catalysts, DMF was found to be the most effective solvent in this coupling reaction to give **3a** in 17% yield. To our delight, the combination of $[RhCp^*Cl_2]_2$ and $Cu(OAc)_2{\cdot}H_2O$ in DMF promoted the coupling of **1a** and **2a** to provide our desired product **3a** in 62% yield. After further optimization, we found that the AcOH additive facilitated high levels of catalytic activity. Thus the best results were obtained by the use of 2.5 mol % of $[RhCp^*Cl_2]_2$ and 200 mol % of $Cu(OAc)_2{\cdot}H_2O$ in DMF/AcOH (3:1) solvents under otherwise identical conditions, affording the desired isoindoline **3a** in high yield (91%).

With the optimized reaction conditions in hand, the scope and limitation of *N*-benzyltriflamides were examined (Table 1). The coupling of *ortho*-substituted *N*-benzyltriflamides **1b**–**1e** and *n*-butyl acrylate (**2a**) was found to be favored in the olefination and

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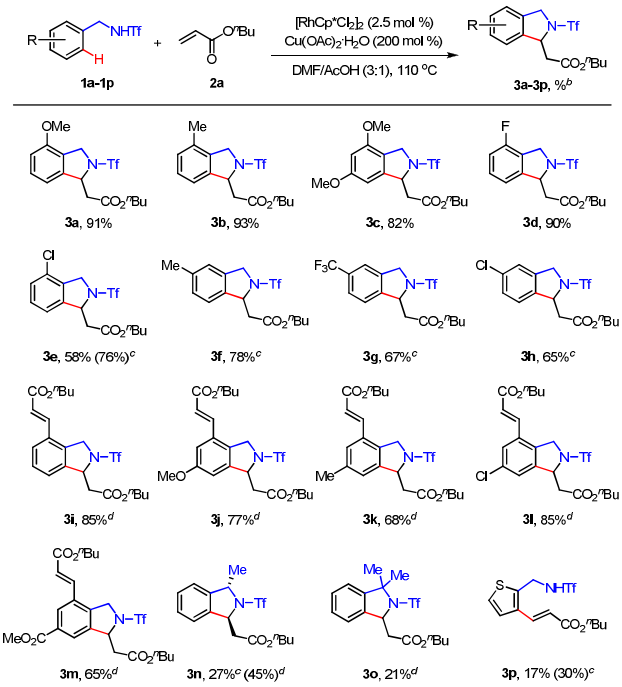
subsequent cyclization reaction to afford our desired products **3b**–**3e** in high yields. This reaction was also compatible with *meta*-substituted *N*-benzyltriflamides **1f**–**1h** in the presence of 200 mol % of **2a** for 40 h furnishing the corresponding products **3f**–**3h** in good yields. Particularly noteworthy was the regioselectivity occurring at the more sterically accessible position and the tolerance of the reaction conditions to chloro moiety, which provides a versatile synthetic handle for further functionalization of the products. Subsequently, we tried to perform the coupling reaction between symmetrical *N*-benzyltriflamide **1i** and acrylate **2a** under the optimal reaction conditions, but we obtained a mixture of isoindolines derived from mono- and bis-olefination. Thus, compounds **1i**–**1m** were treated with 4 equiv. of **2a** for 40 h under otherwise identical conditions to afford the 4-alkenylated isoindolines **3i**–**3m** in good to high yields. In addition, α-substituted *N*-benzyltriflamides **1n** and **1o** displayed a relatively decreased reactivity under the present reaction conditions. In contrast, the reaction of **1p** with **2a** provided the alkenylated compound **3p** and no further aza-Michael reaction took place.[10]

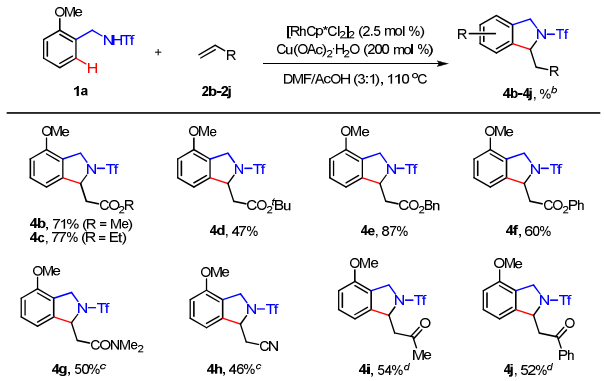
Table 1 Scope of *N*-benzyltriflamides[a]



[a] Reaction conditions: **1a**–**1p** (0.3 mmol), **2a** (0.45 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (200 mol %), DMF/AcOH (3:1, 1 mL), 110 °C for 24 h in sealed tubes. [b] Yield isolated by column chromatography. [c] **2a** (0.6 mmol), 40 h. [d] **2a** (1.2 mmol), 40 h.

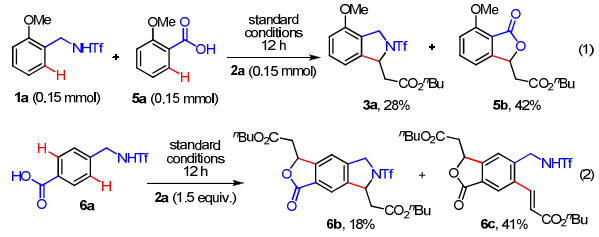
To further explore the substrate scope and limitations, a range of olefins **2b**–**2j** was screened to couple with **1a** under optimal reaction conditions, as shown in Table 2. To our pleasure, olefins **2b**–**2h** with electron-withdrawing groups proved to be good substrates for this transformation, affording the corresponding products **4b**–**4h**. Interestingly, α,β-unsaturated ketones **2i** and **2j** gave a separable mixture of isoindolines (4% for **2i** and 16% for **2j**) and the alkylated compounds (20% for **2i** and 55% for **2j**) under DMF/AcOH conditions (see Supplementary Information for the details).[19] After further optimization, we found that MeCN solvent provided our desired products **4i** and **4j** as the major compounds in satisfactory yields. Further reductive cleavage of triflate group of **3a** using $LiAlH_4$ was performed to give the corresponding free (NH)-isoindoline in 72% yield. (see Supplementary Information for the details).

Table 2 Scope of olefins[a]



[a] Reaction conditions: **1a** (0.3 mmol), **2b**–**2j** (0.45 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (200 mol %), DMF/AcOH (3:1, 1 mL), 110 °C for 24 h in sealed tubes. [b] Yield isolated by column chromatography. [c] **2g** and **2h** (0.6 mmol). [d] MeCN was used as a solvent.

Encouraged by these results, we further examined the intermolecular and intramolecular competition experiments between our triflamide group and carboxylic acid group reported by Satoh and Miura,[8] as shown in Scheme 2.



Scheme 2 Competition experiments.

First, intermolecular competition experiment between *N*-(2-methoxybenzyl)triflamide (**1a**) and 2-methoxybenzoic acid (**5a**) was conducted under the standard reaction conditions. Exposure of 1 equiv. of *n*-butyl acrylate (**2a**) to equimolar quantities of **1a** and **5a** provided a separable mixture of isoindoline **3a** (28%) and phthalide **5b** (42%), respectively. Intramolecular competition experiment of **6a** with both triflamide and carboxylic acid groups under otherwise identical conditions afforded a mixture of **6b** (18%) and **6c** (41%). Based on these results, it is indicated that carboxylic acid moiety might be more rapidly involved in C–H bond activation and intramolecular cyclization process.

To gain a mechanistic insight of these reactions, the following experiments were conducted (Scheme 3). A hydrogen/deuterium exchange experiment using AcOD showed that the cleavage of the *ortho*-C–H bond was a reversible metalation–proto(deutero)demetalation process. To further probe the role of rhodium catalyst, copper salt and AcOH, several experiments were performed. A trace amount of **3a** was obtained without using copper acetate or AcOH (condition A), while 71% and 95% yields of **3a** were isolated in the absence of Rh catalyst

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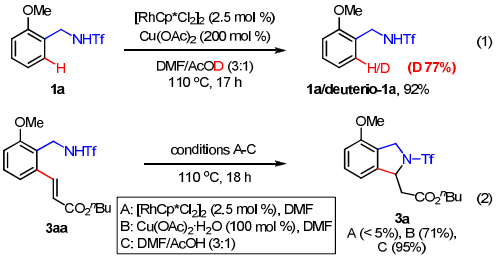
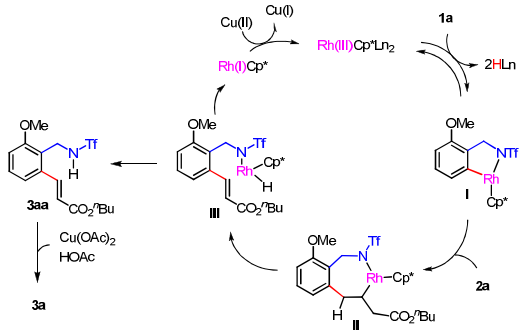
(conditions B and C), which indicated that $Cu(OAc)_2 \cdot H_2O$ or AcOH is crucial to facilitate intramolecular cyclization.



Scheme 3 Mechanistic studies.

On the basis of collective data, a plausible reaction mechanism is proposed as illustrated in Scheme 4. First, a coordination of triflamide **1a** to a Rh(III) catalyst facilitate the formation of a rhodacycle **I**, which can undergo a migratory insertion of olefin **2a** to generate intermediate **II**. Subsequently, the β-H elimination of **II** followed by reductive elimination affords compound **3aa** and a Rh(I) species, which is then reoxidized by Cu(II) to regenerate Rh(III). The formed olefin **3aa** presumably reacts with Cu(II) or AcOH to undergo the aza-Michael addition[5g,10,17a,20] followed by subsequent enolate protonation to give isoindoline **3a**.



Scheme 4 Proposed reaction mechanism.

In conclusion, we developed the facile and efficient strategy for the construction of isoindolines via rhodium(III)-catalyzed oxidative *ortho*-alkenylation of *N*-benzyltriflamides with olefins followed by intramolecular cyclization.

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