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Nickel-Catalyzed Annulation of Aliphatic Amides with Alkynylsilanes: An Expeditious Approach to Five-Membered Lactams

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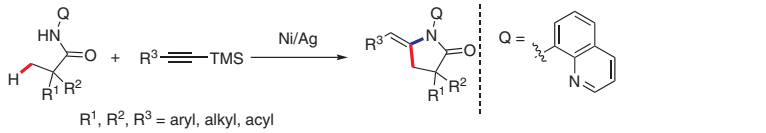

- *E*-configuration
- inexpensive Ni(II) as the catalyst
- aliphatic amides/alkynylsilanes = 1:1
- tolerance of various aliphatic amides and alkynylsilanes
- 23 examples, up to 99% yield

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Abstract An expeditious approach for the synthesis of diverse five-membered lactams through nickel-catalyzed annulation of the C(sp^3)–H bonds of aliphatic amides with alkynylsilanes assisted by an 8-aminoquinolinyl directing group is reported, delivering the corresponding lactam derivatives in moderate to high yields. It is worth noting that alkynylsilanes are employed for the first time as coupling partners in the transition-metal-catalyzed functionalization of C(sp^3)–H bonds of aliphatic amides. Equimolar amounts of alkynylsilanes and aliphatic amides are utilized, which greatly increases the efficiency of this protocol.

Key words five-membered lactams, nickel-catalyzed, annulations, C(sp^3)–H bonds, aliphatic amides, alkynylsilanes

Over the past few decades, significant headway has been made in the transition-metal-catalyzed direct functionalization of C–H bonds, and the process is widely used to construct diverse C–C and C–X bonds as well as synthetically useful heterocycles.[1] Among the many useful heterocycles, lactams represent an important structural motif that occur in a wide range of biologically active compounds, pharmaceuticals and in natural products.[2] In recent years, the annulation of C(sp^2)–H bonds has aroused considerable attention due to the significant value of the synthesis of lactams in organic chemistry.[3] In contrast, protocols involving the direct functionalization of inert sp^3 C–H bonds are limited. An initial study on the synthesis of five-membered lactams through palladium-catalyzed alkenylation/Michael addition of aliphatic amides with electron-deficient alkenes was described by Yu and co-workers in 2010.[4] Later on, the transition-metal-catalyzed intramolecular aminations of the C(sp^3)–H bonds of aliphatic amides for the formation of four- or five-membered lactams were successfully developed by the groups of Chen,[5] Shi,[6] Kanai[7] and Ge.[8] The tandem carbonylation/intramolecular amination of aliphatic amides was independently reported by Chatani,[9] Yu,[10] Gaunt[11] and Wang[12] by using different transition-metal catalysts. Recently, Zhang and co-workers demonstrated an efficient approach to prepare five-membered lactams through Co- and Ni-catalyzed annulations of aliphatic amides with readily available alkynes and propiolic acids (Scheme 1, a).[13] However, two or more equivalents of the terminal alkynes and propiolic acids were required due to the relatively high reactivity and the tendency of self-dimerization or self-trimerization of the terminal alkynes, resulting in an increase in the cost of the system and a reduction in the efficiency of the reactions. In some cases, alkynylsilanes are better coupling reagents than terminal alkynes, because their unique character is exemplified not only in the silyl protection of the terminal C–H of the acetylene, but also in the ability of the silyl group to dictate and improve the regioselectivity of reactions at the triple bond.[14] Thus, achieving the direct C–H annulation of inert C(sp^3)–H bonds with alkynylsilanes by using inexpensive metal catalysts remains an important challenge.

Nickel has been widely utilized as a catalyst in the realm of C–H bond functionalization owing to its advantages of being a cheap and sustainable metal. Several important breakthroughs have been achieved in terms of nickel-catalyzed C–H activation to construct C–C and C–X bonds, as pioneered by Chatani and others,[15] and further underscoring the excellent catalytic performance of nickel catalysts. Recently, a powerful strategy that involved bidentate directing groups proved to be highly efficient in nickel-catalyzed functionalization of inert C(sp^3)–H bonds to realize a variety of useful transformations, including arylation,[16] alkenylation,[15i,j,17] alkynylation,[18] alkylation,[19] intramolecular amination,[8] thioetherification,[20] and annulation.[21] Inspired by these encouraging achievements, we explored an expeditious strategy to prepare five-membered lactams through nickel-catalyzed annulation of the C(sp^3)–H bonds of ali-

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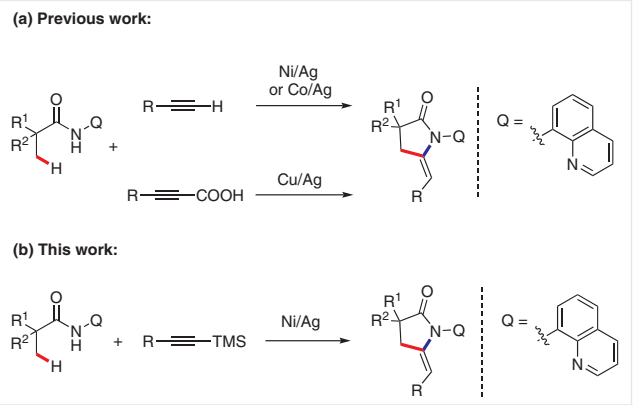


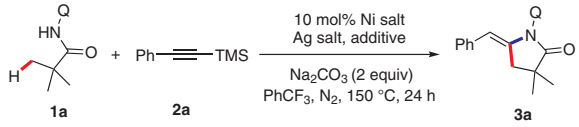
Scheme 1 Transition-metal-catalyzed synthesis of five-membered lactams: (a) previous work, (b) this work

phatic amides with alkynylsilanes assisted by an 8-aminoquinolinyl directing group. Notable features of our strategy include (i) the use of alkynylsilanes[14] as coupling reagents for the first time in the functionalization of C(sp^3)–H bonds, (ii) high functional group tolerance, and (iii) equimolar amounts of alkynylsilanes and aliphatic amides are employed, which greatly increases the efficiency of the process (Scheme 1, b).

Reaction optimization was performed by coupling *N*-(quinolin-8-yl)pivalamide (**1a**) with trimethyl(phenylethynyl)silane (**2a**) as a model system. When the reaction was carried out in the presence of $NiBr_2$, Ag_2CO_3, Na_2CO_3, and TBAI in $PhCF_3$ at 150 °C under an N_2 atmosphere for 24 hours, the desired product **3a** was obtained in a low 11% yield (Table 1, entry 1). Next, other commercially available nickel catalysts were screened, including $NiCl_2$, NiI_2, $(Cy_3P)_2NiCl_2$, $Ni(acac)_2$, and $Ni(OAc)_2$. Gratifyingly, it was observed that $Ni(acac)_2$ showed the best catalytic reactivity, giving the annulated product **3a** in quantitative yield (Table 1, entries 2–6). The replacement of TBAI with other additives had a deleterious effect on the reaction efficiency (Table 1, entries 9–11). Although the exact role of TBAI is unclear at this point, we speculate that it might play the role of a phase-transfer catalyst to increase the solubility of Ag_2CO_3 in $PhCF_3$. An investigation of alternative silver oxidants was also conducted, but lower yields were obtained in each case (Table 1, entries 12–14). Control experiments indicated that the reaction did not occur in the absence of the nickel catalyst, TBAI, the oxidant, or Na_2CO_3, respectively (Table 1, entries 7, 8, 15 and 16). Further optimization with respect to the solvent revealed that $PhCF_3$ was superior compared to other solvents (see the Supporting Information). Furthermore, the yield of product **3a** was reduced when the temperature or the reaction time was decreased (see the Supporting Information).

With optimized reaction conditions in hand, we next investigated the scope of the alkynylsilanes (Scheme 2). Gratifyingly, the results showed that different substituted alky-

Table 1 Optimization of the Reaction Conditions[a]

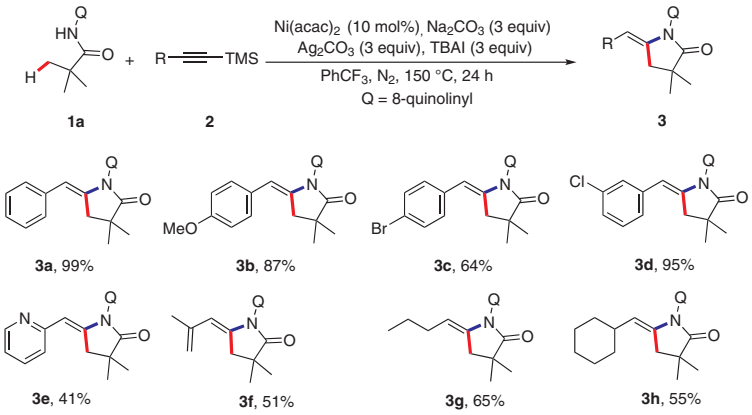


Entry	[Ni]	Ag salt	Additive	Yield (%)[b]
1	$NiBr_2$	Ag_2CO_3	TBAI	11
2	$NiCl_2$	Ag_2CO_3	TBAI	trace
3	NiI_2	Ag_2CO_3	TBAI	20
4	$(Cy_3P)_2NiCl_2$	Ag_2CO_3	TBAI	51
5	**$Ni(acac)_2$**	**Ag_2CO_3**	**TBAI**	**99**
6	$Ni(OAc)_2$	Ag_2CO_3	TBAI	52
7	–	Ag_2CO_3	TBAI	0
8	$Ni(acac)_2$	Ag_2CO_3	–	trace
9	$Ni(acac)_2$	Ag_2CO_3	NaI	0
10	$Ni(acac)_2$	Ag_2CO_3	KI	0
11	$Ni(acac)_2$	Ag_2CO_3	CsI	0
12	$Ni(acac)_2$	Ag_2SO_4	TBAI	33
13	$Ni(acac)_2$	AgOAc	TBAI	26
14	$Ni(acac)_2$	Ag_2O	TBAI	0
15	$Ni(acac)_2$	–	TBAI	0
16[c]	$Ni(acac)_2$	Ag_2CO_3	TBAI	0

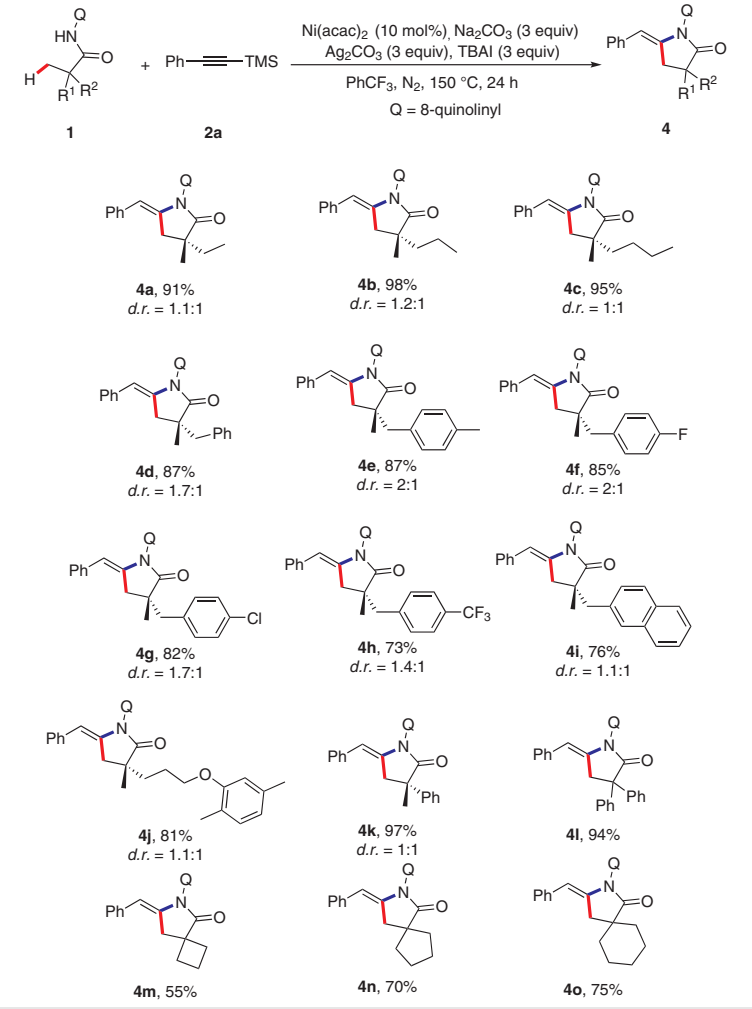
[a] *Reaction conditions*: *N*-(quinolin-8-yl)pivalamide (**1a**) (0.1 mmol), trimethyl(phenylethynyl)silane (**2a**) (0.1 mmol), Ni salt (0.01 mmol), Ag salt (0.3 mmol), Na_2CO_3 (0.3 mmol), additive (0.3 mmol), $PhCF_3$ (1.5 mL), N_2, 150 °C, 24 h. Q = 8-Quinolinyl, TBAI = tetrabutylammonium iodide.
[b] Yield of isolated product.
[c] Without Na_2CO_3.

nylsilanes **2**, including examples with phenyl and alkyl groups, were all compatible under the present reaction conditions, giving the corresponding products **3a–d**,**g–h**. It was worth mentioning that a conjugated alkynylsilane could participate in this transformation to provide the corresponding lactam-containing conjugated diene **3f**, which may allow the synthesis of more complex molecules. More significantly, 2-[(trimethylsilyl)ethynyl]pyridine was also applicable under the current reaction conditions, affording the desired product **3e** in a moderate 41% yield.

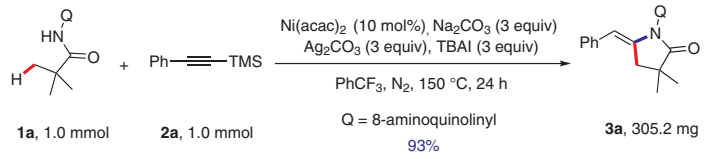
After examining the compatibility of the annulation reaction with a variety of alkynylsilane substrates, our attention turned toward the reactivity of different aliphatic amides **1** (Scheme 3). A variety of aliphatic amides bearing a β-methyl group smoothly participated in the annulation reaction to provide the corresponding *E*-configured products **4a–o** in moderate to excellent yields. Different substituents located at the α-carbon of the aliphatic amides, such as alkyl, benzyl, and even phenyl, were all tolerated in the transformation. Noteworthy was the fact that the formation of two racemic pairs of enantiomers of **4a–k** were observed with regard to the different substituents at the α-carbon of



Scheme 2 Substrate scope of the alkynylsilanes. *Reaction conditions*: **1a** (0.1 mmol), alkynylsilane **2** (0.1 mmol), $Ni(acac)_2$ (0.01 mmol), Ag_2CO_3 (0.3 mmol), Na_2CO_3 (0.3 mmol), TBAI (0.3 mmol), $PhCF_3$ (1.5 mL), N_2, 150 °C, 24 h. Yields of isolated products are given



Scheme 3 Substrate scope of the aliphatic amides. *Reaction conditions*: **1** (0.1 mmol), trimethyl(phenylethynyl)silane (**2a**) (0.1 mmol), $Ni(acac)_2$ (0.01 mmol), Ag_2CO_3 (0.3 mmol), Na_2CO_3 (0.3 mmol), TBAI (0.3 mmol), $PhCF_3$ (1.5 mL), N_2, 150 °C, 24 h. Yields of isolated products are given

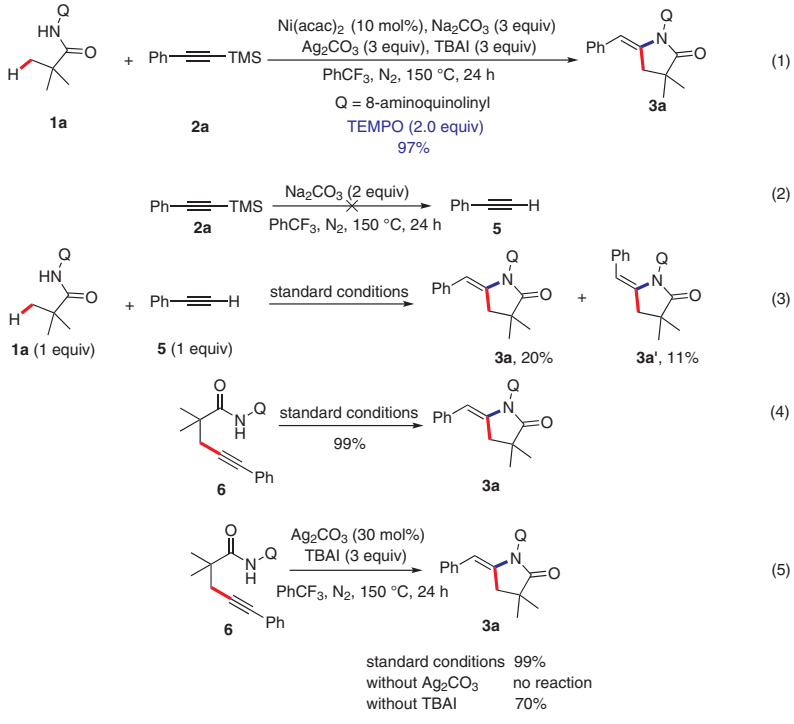


Scheme 4 Sub-gram-scale synthesis of **3a**

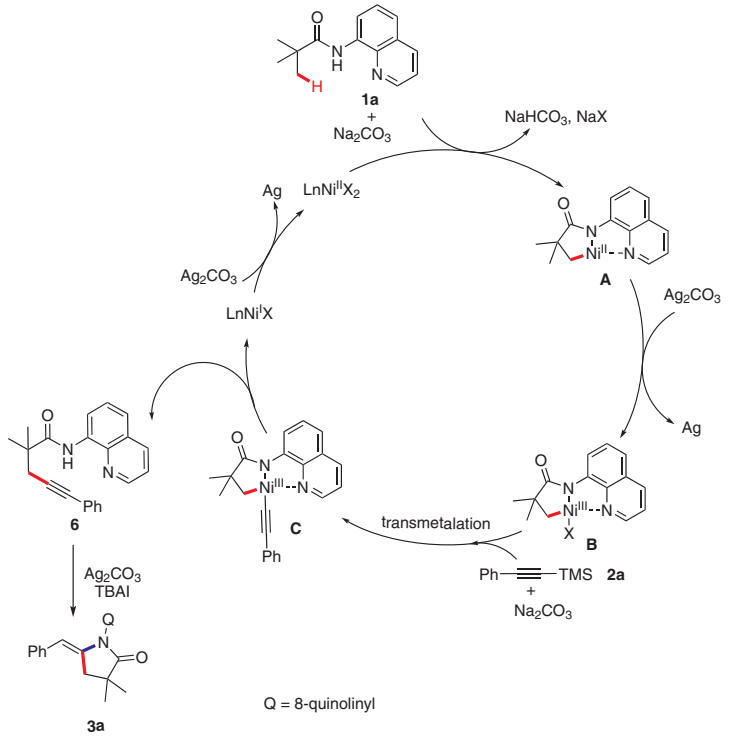
the aliphatic amides, presumably due to axial chirality arising from hindered rotation around the N1–C(quinolinyl) bond.[13] It is worth mentioning that the site of C(sp^3)–H annulation occurred exclusively at the β-methyl group instead of the β-methylene or γ-methyl groups of the amides, thereby demonstrating the high regioselectivity of the protocol. The reason that the annulation does not occur at the methylene C(sp^3)–H bonds may be due to the fact that such bonds are more inert and sterically hindered compared with methyl C(sp^3)–H bonds. Several α-cyclic amides were also compatible with the reaction system leading to the corresponding spiral lactam products **4m–o** with moderate efficiency.

Importantly, when the reaction was scaled up to 1.0 mmol on a sub-gram scale, the lactam product **3a** was isolated in 93% yield without any decrease in the efficiency of the reaction, indicating the robustness of our protocol and the potential synthetic applications of this method (Scheme 4). Unfortunately, the desired reaction did not occur when we removed the directing group from the aliphatic amide **1**.

To gain insights into the reaction mechanism, we carried out several control experiments (Scheme 5). The addition of a radical scavenger such as TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) hardly had any influence on the reaction, revealing that a radical mechanism for this reaction may be excluded (Scheme 5, eq 1). In addition, the reaction of trimethyl(phenylethynyl)silane (**2a**) with Na_2CO_3 was performed and ethynylbenzene (**5**) was not isolated (eq 2). Besides, ethynylbenzene (**5**) was able to react with substrate **1a** under the standard conditions to give a mixture of products **3a** and **3a′**, albeit in low yield (eq 3). This result illustrated that ethynylbenzene (**5**) was not a suitable annulation coupling partner. Therefore, the mechanism of this reaction is different to that previously reported by Zhang.[13] According to a reported method,[22] we prepared the alkynylated product **6**, which reacted under the standard conditions to form the pyrrolidinone **3a** in 99% yield with *E*-configuration (eq 4). It was thus speculated that the alkynylated product **6** was a key intermediate in the reaction. Further studies revealed that the use of Ag_2CO_3 was essential for the cyclization process to occur (eq 5).



Scheme 5 Control experiments



Scheme 6 A plausible catalytic cycle

Based on these mechanistic results and previous reports,[13,18,21] a plausible catalytic cycle is depicted in Scheme 6. First, the cyclometalation of **1** with Ni(II) generates intermediate **A** with the assistance of the 8-aminoquinoline auxiliary. Subsequent oxidation of Ni(II) to Ni(III)[21] and transmetalation with trimethyl(phenylethynyl)silane (**2a**) forms the intermediate **C**, which undergoes reductive elimination to give the alkynylated product **6**. Oxidation of Ni(I) generates the Ni(II) species through protonation to fulfill the cycle. The silver salt in combination with TBAI promotes the cyclization of alkynylated product **6** to deliver the final product.

In summary, we have reported a highly efficient method for the direct nickel-catalyzed annulation of the C(sp^3)–H bonds of aliphatic amides with alkynylsilanes using an 8-aminoquinolinyl auxiliary as a directing group to deliver diverse, structurally complex five-membered lactam derivatives.[23] Notable features of this protocol include broad substrate scope, excellent regioselectivity and good functional group compatibility. More significantly, alkynylsilanes have been employed for the first time as coupling partners in the transition-metal-catalyzed functionalization of C(sp^3)–H bonds of aliphatic amides. Further mechanistic studies and investigations on extending the method to a range of other coupling partners are currently underway in our laboratories.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610756.

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(23) **Lactams 3 and 4; General Procedure**

A 25 mL sealed tube was charged with 2,2-disubstituted *N*-(quinolin-8-yl)propionamide **1** (0.1 mmol), alkynylsilane **2** (0.1 mmol), $Ni(acac)_2$ (2.57 mg, 0.01 mmol), Na_2CO_3 (31.8 mg, 0.3 mmol), Ag_2CO_3 (82.8 mg, 0.3 mmol), TBAI (110.8 mg, 0.3 mmol) and $PhCF_3$ (1.5 mL). The vial was then evacuated, filled with N_2 and the reaction mixture stirred at 150 °C for 24 h. The mixture was then cooled to room temperature, diluted with EtOAc (2 mL), filtered through a Celite pad, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/PE (1:5 to 1:2, v/v), to afford the desired alkylated product **3** or **4**.

(*E*)-5-Benzylidene-3,3-dimethyl-1-(quinolin-8-yl)pyrrolidin-2-one (3a)

Yield: 32.5 mg (99%); yellow solid; R_f = 0.51 (hexane/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.87 (dd, J_1 = 1.2 Hz, J_2 = 3.2 Hz, 1 H), 8.20 (dd, J_1 = 1.2 Hz, J_2 = 6.8 Hz, 1 H), 7.92 (dd, J_1 = 1.2 Hz, J_2 = 6.4 Hz, 1 H), 7.63–7.69 (m, 2 H), 7.41 (dd, J_1 = 3.2 Hz, J_2 = 6.8 Hz, 1 H), 7.21–7.25 (m, 2 H), 7.06–7.10 (m, 3 H), 5.28 (s, 1 H), 3.25 (dd, J_1 = 1.2 Hz, J_2 = 14.4 Hz, 1 H), 3.13 (dd, J_1 = 1.2 Hz, J_2 = 14.4 Hz, 1 H), 1.53 (s, 3 H), 1.43 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.1, 151.1, 144.3, 143.0, 137.0, 136.1, 133.4, 130.4, 129.6, 129.3, 128.3, 127.6, 126.4, 125.2, 121.9, 104.4, 41.2, 40.9, 26.1, 25.7. HRMS (EI-TOF): *m*/*z* $[M]^+$ calcd for $C_{22}H_{20}N_2O$: 328.1576; found: 328.1574.