C–H Amidation Hot Paper

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Iridium-Catalyzed Direct C–H Amidation with Weakly Coordinating Carbonyl Directing Groups under Mild Conditions**

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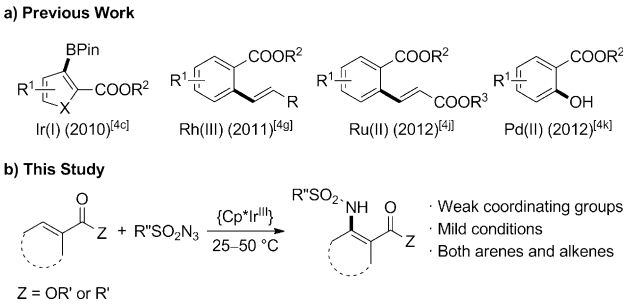
Abstract: *An iridium-catalyzed direct C–H amidation of weakly coordinating substrates, in particular of those bearing ester and ketone groups, under very mild conditions has been developed. The observed high reaction efficiency was achieved by the combined use of acetic acid and lithium carbonate as additives.*

Since the pioneering work of Murai and co-workers,[1] transition-metal-catalyzed direct C–H functionalizations with various directing groups have provided a straightforward tool for the regioselective formation of carbon–carbon and carbon–heteroatom bonds.[2] Whereas strongly coordinating units, including thio, pyridyl, amino, or amide groups, have been widely employed for chelation-assisted C–H bond activation, the use of substrates that bear only weakly coordinating moieties has been much less successful, which is mainly due to the less efficient formation of the key metallacyclic intermediate.[3] In particular, the utilization of esters as directing groups is still rare, even though this functional group is omnipresent in numerous natural products and synthetic compounds. In spite of a few elegant examples (Scheme 1 a),[4] to the best of our knowledge, esters have not been utilized as directing groups for intermolecular direct C–N bond formation. Herein, we describe the Ir(III)-catalyzed direct amidation of aryl and alkenyl C(sp^2)–H bonds using esters and ketones as viable chelating groups under very mild conditions (Scheme 1 b). The results of this work are significant considering that the ester unit may be used as a readily manageable protecting group in organic synthesis,[5] as it can be converted into various functional groups under ambient conditions.[6]



Scheme 1. Direct C–H functionalizations with an ester directing group. Pin = pinacolato.

Cyclometalation can be accelerated by the addition of external bases, such as acetates or carbonates.[7] Whereas these species may assist the formation of metallacycles in a concerted manner, they often detain the generation of catalytically reactive species as they compete with the substrates for coordination sites. On the other hand, the dissociation of anionic ligands from a metal center can be facilitated by acidic additives to lead to unsaturated cationic metal species.[8] For instance, Dixneuf and co-workers reported a Ru^{II}-mediated autocatalytic process, revealing that carboxylic acid additives can enhance the catalytic activity of ruthenium by promoting the dissociation of an acetate ligand from the metal acetate resting species.[8b] In this context, we envisaged that the coordinating efficiency of weakly binding substrates such as esters and ketones towards a metal center could be increased by suppressing the binding affinity of basic ligands with the aid of suitable acid additives.

To examine the above hypothesis, we screened various reaction conditions for the amidation of ethyl benzoate (**1a**) with an equimolar amount of *para*-toluenesulfonyl azide (**2a**) that are based on our recently developed procedures for C–H amidation[9,10] using a {Cp^*Ir^{III}} catalyst system (Table 1; Cp* = pentamethylcyclopentadienyl).[11] When a silver salt, which is required for the generation of a cationic iridium species, was used as the sole additive (entry 1), no reaction occurred. However, the use of certain additional additives was found to initiate the amidation to some extent. Among various bases screened (entries 2–6), the use of LiOAc (7.5 mol%) resulted in a notable increase in product yield at 50 °C (entry 5). Interestingly, the lithium countercation exerts a significantly stronger effect on the transformation than other cations, such as ammonium, sodium, or potassium ions (entries 2–5). Whereas the use of lithium carbonate on its own led to no conversion (entry 6), we were pleased to observe that the combined use of this salt with acetic acid gave an almost quantitative yield (entry 7). Surprisingly, the amidation proceeded even at room temperature, albeit with slightly lower efficiency (entry 8). The use of CF_3COOH instead of AcOH significantly reduced the reaction efficiency (entry 9). A combination of AcOH and LiOAc gave rise to an inferior result (entry 10) compared to $AcOH/Li_2CO_3$

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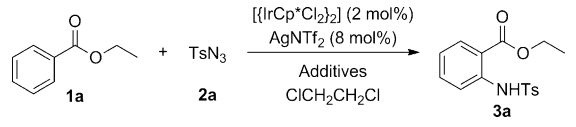
Table 1: Additive screening for the Ir-catalyzed amidation of esters.[a]



Entry	Additive	*T* [°C]	Yield [%]
1	–	50	0
2	NBu_4OAc	50	0
3	NaOAc	50	7
4	KOAc	50	15
5	LiOAc	50	45
6	Li_2CO_3	50	0
7	$AcOH/Li_2CO_3$	50	**98**
8	$AcOH/Li_2CO_3$	**25**	**75**
9	CF_3COOH/Li_2CO_3	50	9
10	AcOH/LiOAc	50	44
11	$B(C_6F_5)_3/Li_2CO_3$	50	0

[a] Conditions: **1a** (0.1 mmol), **2a** (1.0 equiv), [{IrCp*Cl$_2$}$_2$] (2 mol%), $AgNTf_2$ (8 mol%), additives (7.5 mol% in each case), DCE (0.2 M), 12 h (for detailed screening data, see the Supporting Information). DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.

(entry 7). On the other hand, the use of a Lewis acid additive instead of acetic acid was ineffective (entry 11).

As the above optimization results were consistent with our working hypothesis, we could propose a plausible catalytic cycle for the Ir-catalyzed direct C–H amidation of ethyl benzoate (Figure 1). As suggested in our previous studies,[9e,f] upon treatment with a silver salt, a neutral dimeric iridium precursor will first be converted into its cationic monomeric species. A combination of AcOH and Li_2CO_3 will generate lithium acetate and lithium bicarbonate in situ.[12] Considering the weak coordinating ability of an ester group, an acetate ion is expected to coordinate more favorably to the cationic iridium center to form the iridium acetate resting species **A**. Indeed, we could isolate an analogue of complex **A**, namely trifluoroacetato iridium complex **A′**, which bears one molecule of water; its solid state structure was analyzed by X-ray crystallography (Figure 1). Complex **A′** has a piano stool structure with an almost equivalent distance (ca. 2.13 Å) between the iridium center and the five carbon atoms of the Cp* ring. Two CF_3COO^- ligands are coordinated to the iridium center in an η^1 fashion with similar bond lengths (ca. 2.11 Å).

Dissociation of an acetate ligand from **A** leaves one vacant site (**B**) that will subsequently be occupied by an ester group (**C**). The lithium ion is believed to drive the equilibrium forward by abstracting an acetate species as the corresponding salt. C–H bond activation should then occur with the assistance of a bound acetate to afford iridacycle **F** (via **E**), presumably passing through a transition state **D**. In fact, we isolated an analogous iridacycle species, which is derived from an acetophenone derivative (see below). In another crucial step, C–N bond formation will occur upon reversible coordination of the azide to the iridium metal center (**G**), which is followed by an amido insertion process to deliver the desired amidated product with concomitant release of N_2.[13]

We investigated the scope of the amidation with ester-substituted substrates and sulfonyl azides under the optimized conditions at 50 °C (Scheme 2). It should be emphasized that the two reactants, namely ester and azide, were used in an equimolar ratio. Furthermore, for many substrates, satisfactory product yields were obtained even at room temperature. In addition, the reaction was highly selective, and monoamidated products were obtained exclusively without formation of bisamidated by-products.[14]

A broad range of ester-containing substrates was successfully amidated to afford the desired products in good to excellent yields. An electron-rich substrate was amidated with high efficiency even at room temperature (**3b**). Amidation of ethyl 2-naphthoate took place exclusively at the 3-position (**3c**). Functional group tolerance was excellent, as demonstrated by the amidation of bromo- or hydroxy-substituted substrates (**3d** and **3e**). Methoxy and cyclopropyloxy esters were also amidated without difficulty at 50 °C (**3f** and **3g**). Furthermore, lactones with six- or seven-membered rings (**3h** and **3i**) were effective direct-

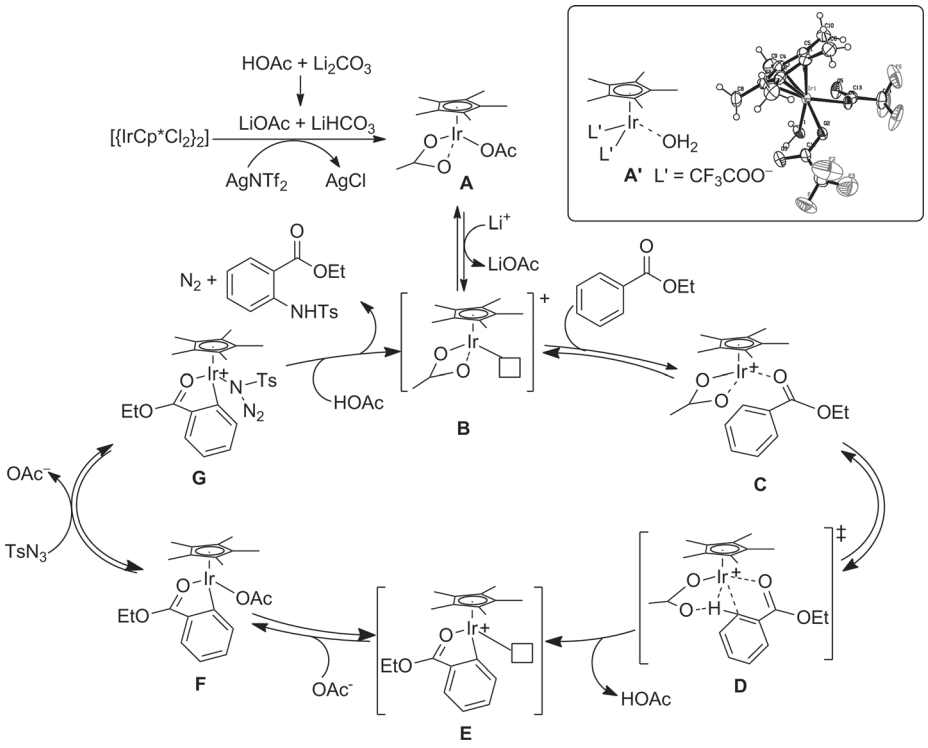
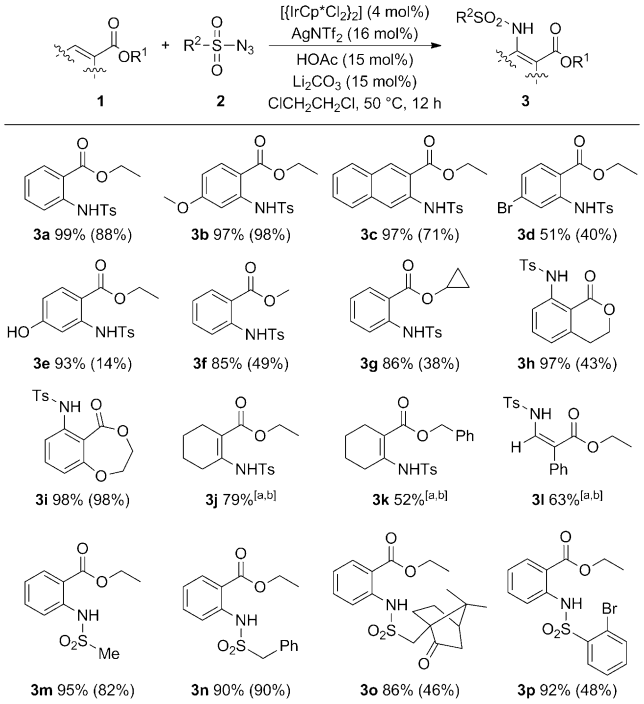


Figure 1. Proposed mechanistic cycle.



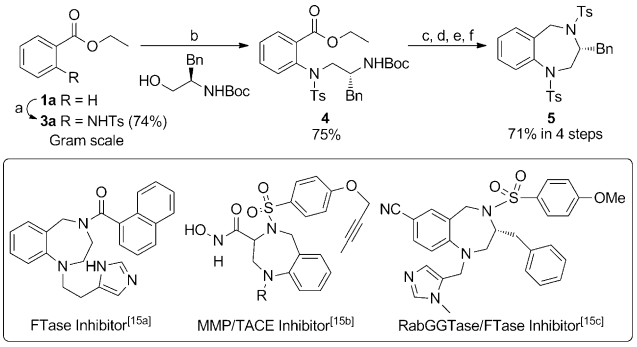
Scheme 2. Scope of the Ir-catalyzed amidation with an ester directing group. Reaction conditions: **1** (0.1 mmol), **2** (1.0 equiv), [{IrCp*Cl_2}$_2$] (4 mol%), $AgNTf_2$ (16 mol%), AcOH (15 mol%), Li_2CO_3 (15 mol%), DCE (0.2 M). Yields of isolated products are given (yields obtained for reactions at room temperature are shown in parentheses). [a] **1** (1.5 equiv). [b] 80 °C.

ing groups to facilitate the desired C–H amidation. Significantly, olefinic C–H bonds could be readily amidated (**3j** and **3k**), which greatly extends the applicability of the present method. 2-Phenylacrylate was selectively amidated at the olefinic C–H bond, while no reaction occurred at the arene moiety (**3l**).

As expected, a wide range of sulfonyl azides were successfully employed as efficient sources for the amide group. Methyl and benzyl variants reacted efficiently even at room temperature (**3m** and **3n**). The amidation of ethyl benzoate with 10-camphorsulfonyl azide was also facile (**3o**). An aryl sulfonyl azide with a bromo group at the *ortho* position was readily utilized in the current amidation, thus allowing for subsequent modifications of the obtained product (**3p**).

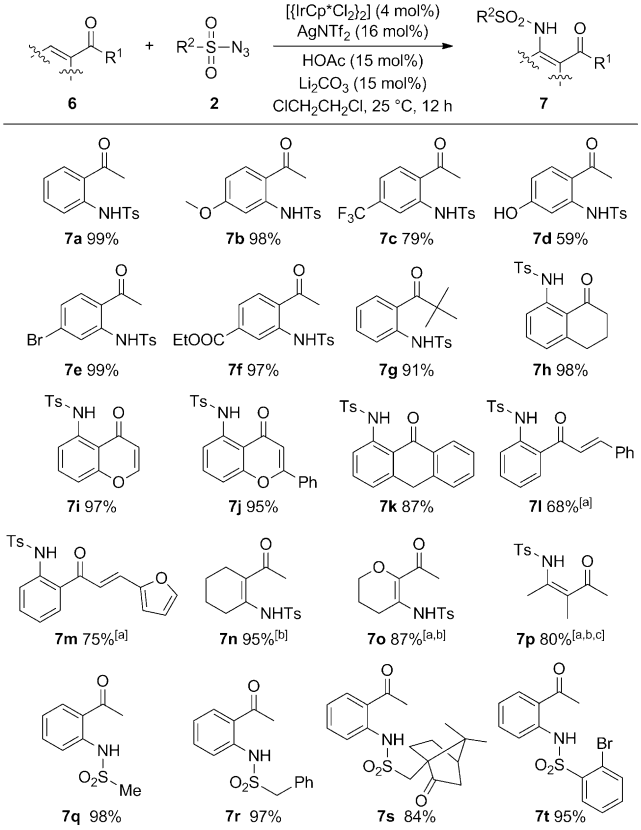
The present method was successfully applied to the synthesis of a benzodiazepine derivative (Scheme 3). The iridium-catalyzed direct C–H amidation of ethyl benzoate (**1a**) could be carried out on a gram scale without difficulty. The secondary amine **3a** was alkylated under Mitsunobu conditions to give **4**, which was then cyclized through four conventional steps, all at ambient temperature, to obtain tetrahydrobenzodiazepine derivative **5**. This molecular skeleton is present in a series of biologically important compounds (Scheme 3).[15]

We next turned our attention to ketone substrates, as this functional group may be employed as another weakly coordinating group with high synthetic utility. We were



Scheme 3. Synthesis of benzodiazepine derivative **5**. a) **1a** (6.67 mmol), **2a** (1.0 equiv), [{IrCp*Cl_2}$_2$] (2 mol%), $AgNTf_2$ (8 mol%), AcOH (7.5 mol%), Li_2CO_3 (7.5 mol%), DCE, 50 °C; b) DEAD, PPh_3, THF, 25 °C; c) HCl (1.5 M), MeOH, 25 °C; d) TsCl, Et_3N, CH_2Cl_2, 25 °C; e) LAH, THF, 25 °C; f) DEAD, PPh_3, THF, 25 °C. Bn = benzyl, Boc = *tert*-butoxycarbonyl, DEAD = diethyl azodicarboxylate, LAH = lithium aluminium hydride.

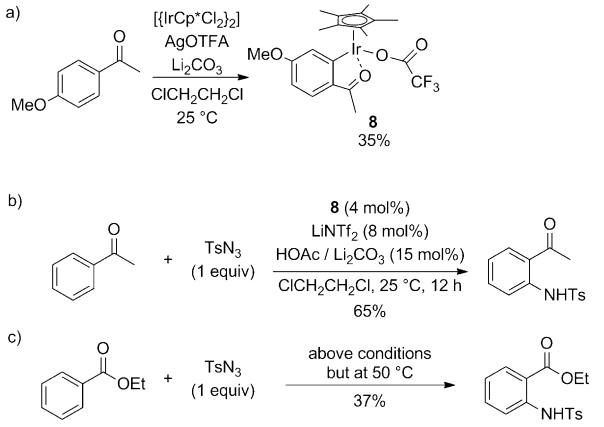
delighted to find that the reaction conditions that had been optimized for ester derivatives were also suitable for the amidation of aryl and olefinic C(sp^2)–H bonds of ketones (Scheme 4). Significantly, most of the examined substrates were amidated smoothly at room temperature in excellent



Scheme 4. Scope of the Ir-catalyzed amidation with a ketone directing group. Reaction conditions: **6** (0.1 mmol), **2** (1.0 equiv), [{IrCp*Cl_2}$_2$] (4 mol%), $AgNTf_2$ (16 mol%), AcOH (15 mol%), Li_2CO_3 (15 mol%), DCE (0.2 M). Yields of isolated products are given. [a] 50 °C. [b] **6** (1.5 equiv). [c] 30 h.

yields. Again, the two reactants, namely ketone derivative and sulfonyl azide, were employed in an equimolar ratio. Acetophenone was amidated in quantitative yield (**7a**). Both electron-withdrawing and -donating substituents hardly influenced the reaction efficiency (**7b** and **7c**). Functional group compatibility was excellent as was demonstrated with hydroxy- (**7d**) and bromo-substituted (**7e**) derivatives. Amidation selectively occurred at the *ortho* position relative to the ketone in the presence of an ester group (**7f**), thus indicating that the former is a more effective chelating group than the latter substituent. The introduction of alkyl substituents on the acetophenone substrate was not detrimental to this transformation (**7g**). Cyclic ketone derivatives were also suitable substrates for arene C–H amidation. Biorelevant molecular skeletons, such as α-tetralone (**7h**), chromone (**7i**), flavone (**7j**), and anthrone (**7k**) derivatives, were all amidated in excellent yields at room temperature.[16] Aryl vinyl ketones were exclusively amidated at the arene ring (**7l** and **7m**). On the other hand, olefinic C–H amidation was viable for alkenyl ketones to give enamides in high yields (**7n**–**7p**). Furthermore, an acyclic olefinic ketone was readily amidated to afford *Z* enamide **7p**, although a longer reaction time was required. All of the examined sulfonyl azides were found to be suitable substrates for the iridium-catalyzed amidation of acetophenone at room temperature (**7q**–**7t**).

To shed light on the mechanistic aspects of the present C–H amidation reaction, we first tried to obtain iridacyclic intermediates that are derived from weakly coordinating substrates. We were delighted to be able to isolate metallacycle **8** of 4-methoxyacetophenone (**6b**) when AgOTFA and Li_2CO_3 were used as additives (Scheme 5a; TFA = trifluoroacetyl). To the best of our knowledge, its single-crystal



Scheme 5. Formation of iridacycle complex **8** and its catalytic reactivity.

structure is the first one that has been obtained for a discrete iridacycle generated from a ketone compound, although there are some examples of the corresponding Pd complexes (Figure 2).[4k,17] The distance between the iridium center and the carbonyl oxygen atom is 2.14 Å, which is similar to that between the iridium and trifluoroacetato oxygen atoms (2.12 Å). The distance between iridium and aryl carbon atom is 2.04 Å, and the chelate bite angle is 78.0°. Two of the

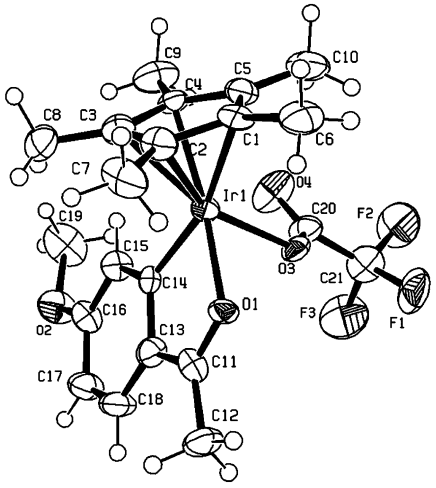
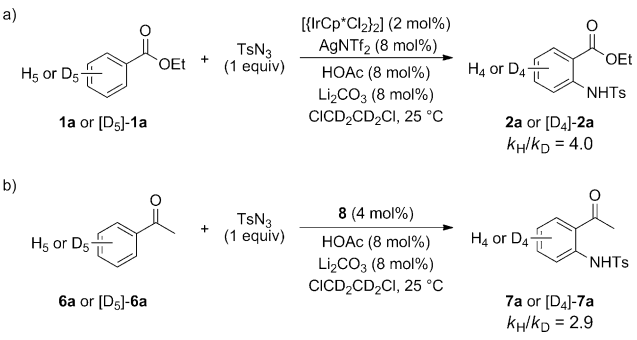


Figure 2. Crystal structure of complex **8**. Ellipsoids set at 50% probability.

Ir–C bonds (2.24 Å) to the Cp* ring are slightly longer than the remaining three (2.14, 2.14, and 2.16 Å), presumably owing to a different *trans* influence of the three other ligands, as reported previously.[18] The catalytic activity of **8** was subsequently investigated for the amidation of acetophenone (Scheme 5b) and ethyl benzoate (Scheme 5c). Whereas the amidated acetophenone derivative was obtained in high yield at room temperature, the reaction of ethyl benzoate proceeded with lower efficiency. This result strongly suggests that an iridacyclic intermediate is involved in the catalytic cycle of the current amidation reaction.

The initial amidation rates of normal substrates and their deuterated analogues were also examined. A primary kinetic isotope effect (KIE; $k_H/k_D = 4.0$) was observed for the amidation of ethyl benzoate and its deuterated derivative (Scheme 6a), implying that C–H bond cleavage is likely to be a rate-limiting step. Interestingly, a significant KIE value ($k_H/k_D = 2.9$) was also measured for acetophenone derivatives, in this case by using iridacyclic species **8** as the catalyst (Scheme 6b).

In summary, we have described the iridium-catalyzed direct intermolecular C–H amidation of weakly coordinating substrates, particularly of ester and ketone derivatives. The reaction exhibits a broad substrate scope and proceeds under



Scheme 6. KIE measurements for the amidation of ester and ketone substrates.

very mild conditions with excellent functional group tolerance. This amidation of weakly coordinating substrates could be achieved by the combined use of acetic acid and lithium carbonate, and the role of these additives was proposed with respect to mechanistic aspects. Another attractive feature of this present study is the facile conversion of ester and ketone directing groups, which offers new opportunities in diverse areas, including organic synthesis, medicinal chemistry, and materials science.

Experimental Section

Representative procedure: Ethyl benzoate (**1a**, 0.1 mmol), *para*-toluenesulfonyl azide (**2a**, 0.1 mmol), [{IrCp*Cl_2}$_2$] (3.2 mg, 4 mol%), $AgNTf_2$ (6.2 mg, 16 mol%), Li_2CO_3 (1.1 mg, 15 mol%), AcOH (0.90 mg, 15 mol%) and 1,2-dichloroethane (0.5 mL) were placed in a screw-capped vial equipped with a Spinvane triangular stir bar under argon atmosphere. The reaction mixture was stirred at 50 °C in a pre-heated oil bath for 12 hours, cooled to room temperature, filtered through a pad of celite and silica gel, and washed with CH_2Cl_2 (3 × 10 mL). The solvents were removed in vacuo, and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 5:1, v/v) to give **3a** (31.6 mg, 99%).

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