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# A solely-Fe-catalyzed Sonogashira-type coupling of non-activated secondary alkyl iodides with terminal alkynes

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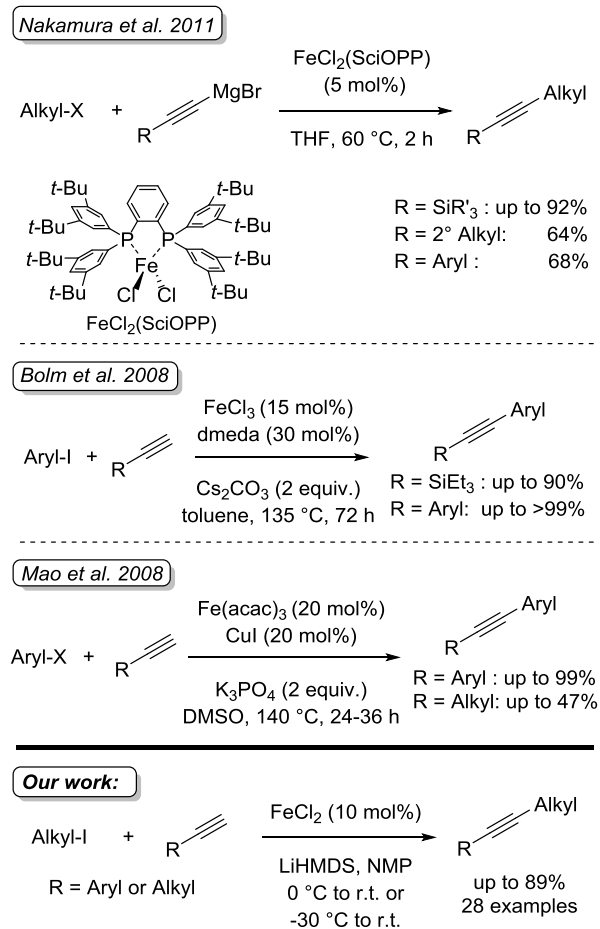
<sup>‡</sup> These authors contributed equally to this work.

**Abstract.** An iron-catalyzed Sonogashira coupling of non-activated secondary alkyl iodides with terminal alkynes is described. The reaction proceeds under mild conditions in *N*-Methylpyrrolidone without auxiliary ligand or co-catalyst. This procedure allowed the obtention of 28 coupling products. Moreover, slow addition of LiHMDS base allows to achieve up to 89% yields. This method enables the conversion of non-activated alkyl iodides in a Fe-catalyzed Sonogashira-type cross-coupling, which was so far not achievable with iron catalysts. Preliminary mechanistic studies suggest the implication of a key single electron transfer in the catalytic process.

**Keywords:** Iron; Cross-coupling; Alkynes; Radical reactions

Formation of C<sub>sp</sub>-C bonds is a pivotal transformation in organic synthesis. Substituted alkynes are indeed ubiquitous, key intermediates in multistep transformations, or present per se in products of interest, with applications ranging from medicine to electronic materials.<sup>[1,2]</sup> Such linkage can easily be obtained within a classic Sonogashira cross-coupling reaction, relying on the palladium-catalyzed coupling of a terminal alkyne with an organic halide in the presence of copper as co-catalyst and a base.<sup>[3,4]</sup> Finding catalytic systems employing non-noble metal-based catalysts and cheap ligands, or, ideally, ligand-free systems, rather than more expensive palladium complexes remains challenging. To date, some Ni- and Cu catalyzed Sonogashira couplings were reported, however alkyl-Sonogashira coupling remains challenging.<sup>[5-14]</sup> Notably, Liu and co-workers reported a Sonogashira coupling of unactivated secondary alkyl iodides catalyzed by a nickel – PyBox complex in the presence of CuI. However, difficult-to-handle Ni(cod)<sub>2</sub> as nickel source was necessary to achieve high yields, and requires a copper co-catalysis. Without the latter the yield drops from 95% to 15% for the model substrate. Moreover, a series of functionalized substrates gave moderate (35-63%) yields. The authors also claim that the Ni complex previously reported by Hu *et al.*<sup>[6]</sup> for Sonogashira-type coupling of primary alkyl halides failed if a secondary alkyl iodide such as iodocyclohexane was employed.<sup>[8]</sup>

## Previous works:



**Scheme 1.** Iron-catalyzed Sonogashira-type coupling of organic halides.

Amongst the 3rd-row transition metals, iron is an appealing alternative to palladium in cross-coupling reactions, with advantages of being cheap, non-toxic, and abundant. Representative examples of iron-catalyzed Sonogashira reactions are summarized on the Scheme 1. They are mostly limited to aryl iodides<sup>[15-20]</sup> and usually require the presence of a ligand such as a phosphine or a bidentate *N,N*-ligand, copper as co-catalyst, high temperatures (over 100 °C) and prolonged reaction time. So far, non-activated secondary alkyl halides remain challenging substrates for Fe-catalyzed Sonogashira chemistry, due to the proficiency of β-elimination side reactions occurring in those substrates. In fact, the only known example is a Sonogashira-type cross-coupling

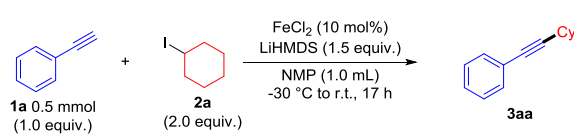
catalyzed by an iron complex based on a bulky bidentate phosphine ligand SciOPP (Scheme 1) reported by Nakamura and co-authors.<sup>[21]</sup> However, this methodology relies on alkynyl Grignard reagents as starting materials rather than alkynes themselves.

We were therefore challenged to develop an iron-catalyzed Sonogashira coupling involving non-activated alkyl halides. We report in this work that Sonogashira cross-coupling with secondary alkyl iodides as electrophilic partners and a variety of terminal alkynes can be achieved using FeCl<sub>2</sub> as an iron source. It is of note that this method does not require the use of an exogenous ligand, and affords up to 89% of cross-coupling product under mild conditions (-30 °C to 0 °C or room temperature), leading overall to a cheap, atom-economic system relying on an abundant metal as a single catalyst.<sup>[22]</sup>

To start the optimization process, we chose a model system using phenylacetylene **1a** and iodocyclohexane (CyI) **2a** as coupling partners (Table 1). We found that the presence of *N*-methylpyrrolidone (NMP) as solvent and LiHMDS as base were essential for the reaction (57% isolated **3aa** was reproducibly obtained, Table 1, Entry 1). This yield has been reproduced on three runs to rule out any effect of impurities present in the vessel (run 1: use of disposable GC vials to carry out the reaction; run 2: use of new magnetic stir bar; run 3: use of a classic round-bottom flask treated with *aqua regia* prior to the reaction). No trace of coupling product was obtained when NMP was substituted by either THF, Et<sub>2</sub>O or toluene (entries 2-4). No coupling product was obtained when *N*-MethylCaProLactam (NMCPL; hexahydro-1-methyl-2*H*-azepin-2-one) was used as a less toxic cyclic amide solvent as an alternative of NMP (Entry 5);<sup>[23]</sup> this may be due to some solubility issues of the ferrous salt in the former solvent. It is noteworthy that even a small (<10% v/v) added quantity of NMP is enough to unblock the product formation (entry 6). Hence, NMP coordination to either Fe or Li may play a role in the formation or the stabilization of on-cycle species. Moreover, respectively 13% and 7% coupling yield were obtained in DMF and DMSO (Entries 7-8). Additionally, no product was observed in the absence of the iron catalyst (Entry 9). It proves that the reaction under study is a truly iron-catalyzed cross coupling (FeCl<sub>2</sub> of 99.99% purity was used exclusively in the experiments to rule out catalysis by metal contaminants<sup>[24]</sup>). To definitively exclude the implication of trace metal impurities in the catalysis, an ICP-MS study of the reaction medium (Entries 1 and 9, Table 1) was performed. Cu levels as high as 6.5 ppm can be detected in both cases (with 58% and 0% product yield), which are likely brought by the Cu beads used as stabilizer in the commercial iodocyclohexane. The absence of the product in the second case proves that these levels of Cu are unable to catalyse the reaction. The same conclusion applies to Co and Ni, which have been detected at a ppb level in starting **2a**. It is of note that Cu, Co and Ni are detected at the same level in reaction media from

Entries 1 and 9, in line with the high purity of Fe precursor which does not bring significant amounts of metal contaminants. Moreover, Pd was beyond detection limit in all cases (see SI). Replacing FeCl<sub>2</sub> with FeBr<sub>2</sub> of equal purity (Entry 10) resulted in a somewhat smaller yield. No coupling product was observed upon substitution of LiHMDS by *t*-BuOK, KH or LiOH (Entries 11-13). Use of other lithium bases such as LiOMe, *n*-BuLi or *t*-BuOLi led to detection of traces of coupling product (3%-8%, Entries 14-16), confirming the crucial role of the lithium cation and the better performances of LiHMDS. An excess (2 equiv. vs **1a**) of electrophile **2a** was required, as showed by Entries 17-18. A poor 8% yield was obtained when CyBr was used (Entry 19), in line with the classic higher reactivity of organic iodides in cross-couplings. Addition of 0.5 equiv. of TEMPO in the reaction medium led to the absence of cross-coupling, suggesting a radical-based mechanism, as discussed in a further section of this report (Entry 20).

**Table 1.** Effect of reaction parameters.



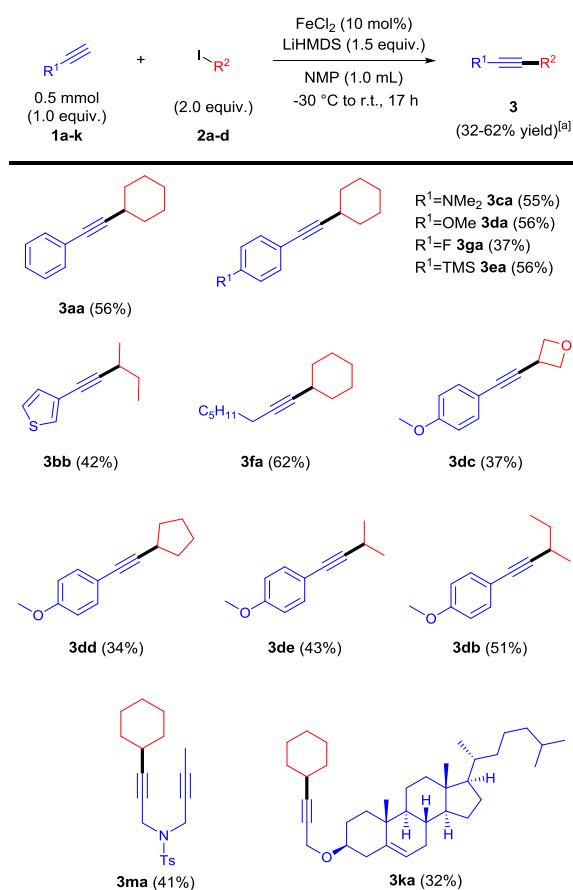
Entry	Deviation from the standard conditions	Yield <b>3aa</b>
1	none	57% <sup>[a]</sup>
2	THF instead of NMP	0
3	diethyl ether instead of NMP	0
4	toluene instead of NMP	0
5	NMCPL instead of NMP	0
6	NMCPL (1.0 mL) + NMP (0.1 mL)	6%
7	DMF instead of NMP	13%
8	DMSO instead of NMP	7%
9	without FeCl <sub>2</sub>	0
10	FeBr <sub>2</sub> instead of FeCl <sub>2</sub>	49%
11	<i>t</i> -BuOK instead of LiHMDS	0
12	KH instead of LiHMDS	0
13	LiOH instead of LiHMDS	0
14	LiOMe instead of LiHMDS	3%
15	<i>n</i> -BuLi instead of LiHMDS	8%
16	<i>t</i> -BuOLi instead of LiHMDS	5%
17	1.5 equiv. of CyI	49%
18	CyI (1.0 equiv, 0.5 mmol) + PhCCH (2.0 equiv.)	45%
19	CyBr instead of CyI	8%
20	with TEMPO 50 mol%	0%

GC yields unless stated otherwise [a] Isolated yield, average yield on 3 experiments; see SI for full optimization table.

The established reaction conditions were applied to a variety of alkynes and alkyl iodides (Scheme 2). Moderate to good yields were obtained for a variety of functionalized substrates. Thiophene derivatives

could be obtained (**3bb**, 42%), and a 55% yield was obtained for *N,N*-dimethylaniline derivative **3ca**; this result is encouraging since thiophenes and substituted amines can often have a poisoning effect on the activity of Fe-based catalysts, leading to their deactivation.

4-Methoxyphenylacetylene **1d** and TMS-substituted **1e** could also be used as coupling partners with a variety of organic iodides (up to 56% yield for both **3da** and **3ea**). Use of 4-membered-ring oxetane (**2c**) or 5-membered-ring (**2d**) electrophiles led to somehow lower yields (34–37%, **3dd** and **3dc**) with this procedure; electron-poor F-substituted alkyne such as **1g** also afforded a modest 37% yield (**3ga**). Aliphatic terminal alkynes also proved to be reactive, with a 62% yield for compound **3fa**. A dissymmetric *N*-tosyl diyne was used as a partner for the reaction and the coupling product **3ma** was obtained in 41% yield, highlighting tolerance of the *N*-Ts group by this methodology. During purification of the reaction products we noticed that considerable amounts of alkyne homo-coupling by-products (R-CC-CC-R) were formed.<sup>[25]</sup> This could explain the moderate



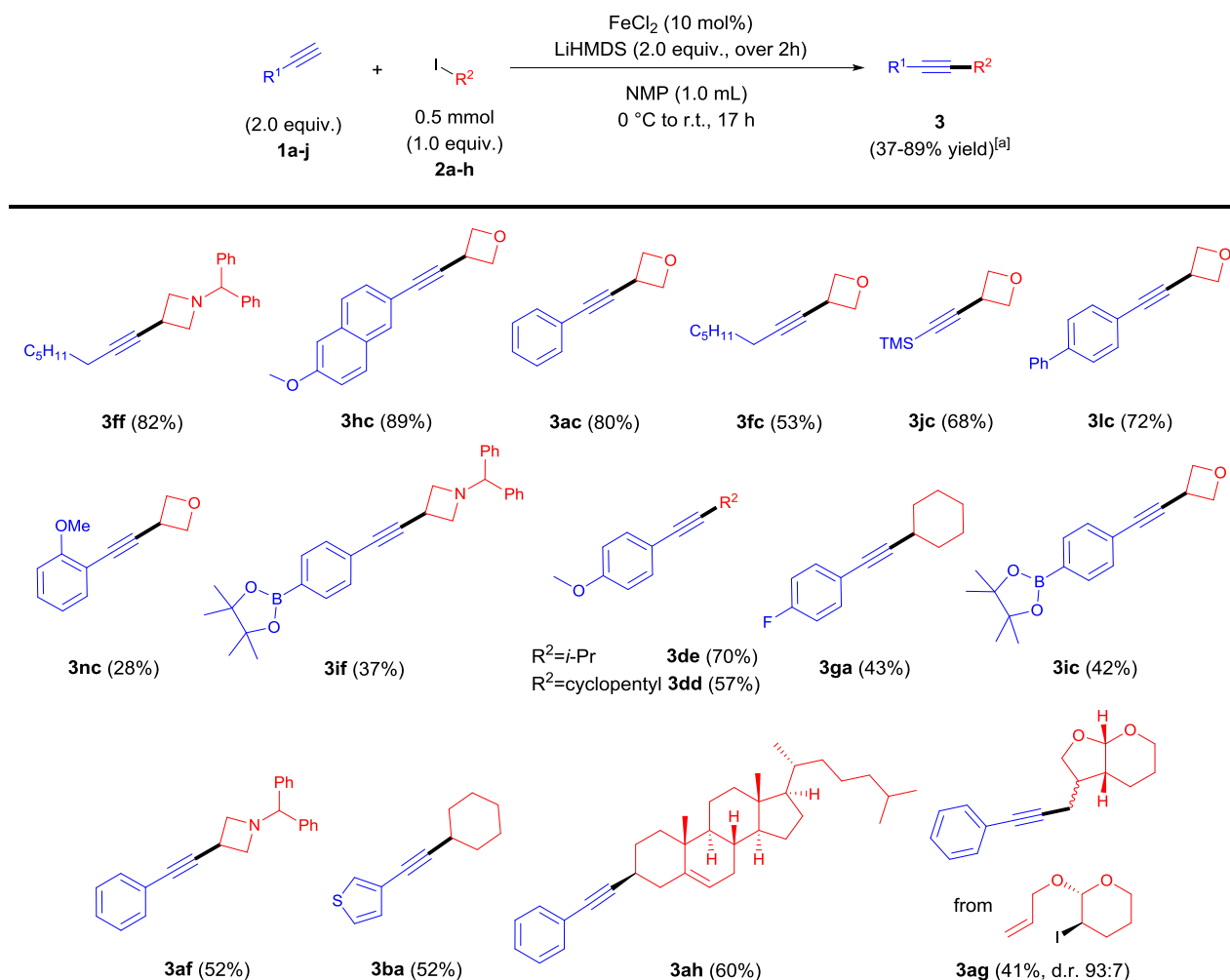
**Scheme 2.** Substrate scope using the conditions of Table 1. Reaction conditions: Alkyne (1.0 equiv.), alkyl iodide (2.0 equiv.), FeCl<sub>2</sub> 10 mol%, LiHMDS (1.5 equiv.), NMP 1 mL, -30 °C to r.t., 17 h [a] Isolated yield.

yields obtained under the conditions presented in Scheme 2. This byproduct may be formed during

activation of the iron pre-catalyst and hence is difficult to avoid. It can also be formed within an oxidative Glaser-type homocoupling off-cycle pathway in which the organic iodide acts as a sacrificial oxidant.

Therefore, we hypothesized that higher yields may be achieved when using the alkyl iodide as limiting reagent with an excess of alkyne. However, in that case, rapid side-reactions such as E2 elimination on the electrophile alkyl chain or reduction may hamper the cross-coupling. Therefore, we chose to employ a slow addition of LiHMDS at 0 °C over approximately 2 hours (Scheme 3).

This modification allowed to obtain the desired products in good to high yields (up to 89%, **3hc**). This is also the first example of an iron-catalyzed cross-coupling between an alkyne and a 3-iodoazetidene derivative (**3ff** (82%), **3if** (37%) **3af** (52%)). The substrates of this kind are of particular interest because of their potential antibacterial and anti-tumor activity,<sup>[26–28]</sup> and they lack of synthetic methodologies for their functionalization.<sup>[29]</sup> The same protocol was applied to a variety of iodoalkanes and alkynes and provided the coupling products with yields ranging from 28% to 89%. Ring-strained 3-iodooxetane was found to be a good electrophilic partner and yielded 80% of **3ac** with phenylacetylene. In the latter case, control experiments in the absence of iron also showed the absence of cross-coupling product, and the ICP-MS analyses for Cu, Co, Ni and Pd contaminants are in line with those performed in the optimization table (see SI). The use of aliphatic alkynes, *n*-octyne in that case, yielded 53% of the product **3fc**. 4-Ethynylbiphenyl was successfully coupled with the 3-iodooxetane in 72% yield (**3lc**). A more sterically hindered alkyne was used, namely the 2-ethynyl-6-methoxynaphtalene, and proved to be the most suitable nucleophilic partner for the reaction with 89% yield (**3hc**). However, use of hindered *ortho*-substituted aryl alkynes was detrimental to the reaction (**3nc**, 28%). A good 68% yield was obtained with the use of trimethylsilyl acetylene (**3jc**), which highlights the fact that this procedure can be used in the presence of multifunctional organosilicon compounds. With this in mind, arylpinacolborane alkyne derivatives were studied next. The pinacol borane moiety was tolerated by our strategy, nonetheless lower yields of 37% and 42% for respectively 1-diphenylmethyl-3-iodoazetidene (**3if**) and 3-iodooxetane (**3ic**) were obtained. Again, thiophene derivatives were also tolerated by this method, and **3ba** was obtained in 52% yield. Protocol displayed in Scheme 3 (two equivalents of alkyne vs alkyl iodide) provided coupling yields for **3de** (70%), **3dd** (57%) and **3ga** (43%) higher than that was obtained when the electrophile was used in excess (resp. 43%, 34%, 37%, Scheme 2). Depending on the relative cost and accessibility of both electrophilic and nucleophilic partners in complex syntheses, it can be of interest to be able to use an excess of the cheapest of the coupling partners. For this purpose,



**Scheme 3.** Substrate scope for alkyl iodide as the limiting reagent. Reaction conditions: Alkyl iodide (1.0 equiv.), alkyne (2.0 equiv.),  $\text{FeCl}_2$  10 mol%, LiHMDS (2.0 equiv.), NMP 1 mL, 0 °C to r.t., 17 h [a] Isolated yield.

cholesterol derivatives were synthesized to show the versatility of the process with either one nucleophilic (**1k**) or one electrophilic (**2h**) cholesterol partners, respectively providing **3ka** in presence of iodo-cyclohexane with 32% yield (Scheme 2) and **3ah** in presence of phenylacetylene with 60% yield (Scheme 3).

The cyclized product **3ag** (41% yield, Scheme 3) was obtained from the corresponding radical clock iodoacetal containing a double bond in the proximity of the C-I center. This indicates that the reaction under study likely proceeds through a radical mechanism. This has been further confirmed by the detection of the TEMPO-Cy adduct by HRMS when cross-coupling between **1a** and **2a** was carried out in the presence of TEMPO (Table 1, Entry 20), confirming the involvement of the cyclohexyl radical  $\text{Cy}^\bullet$  in the reaction process (see SI). This is in line

with other Fe-mediated  $\text{C}_{\text{sp}}\text{-C}_{\text{sp}^3}$  cross-couplings, which feature a key electron transfer between an alkynylated- $\text{Fe}^{\text{II}}$  intermediate and the alkyl halide.<sup>[30,31]</sup> Moreover, requirement of a lithium base as well as NMP solvent in this method may also suggest a key effect of NMP-ligated lithium cations<sup>[32]</sup>  $[\text{Li}(\text{NMP})_n]^+$  in the stabilization of active alkynylated species, as it was reported for  $\text{Mg}^{\text{II}}$  cations in  $\text{C}_{\text{sp}^3}\text{-C}_{\text{sp}^2}$  Fe-mediated Kumada cross-couplings.<sup>[33]</sup>

In conclusion, we demonstrated that a Sonogashira-type cross-coupling reaction using non-activated secondary alkyl iodides was achievable with an iron(II) salt as a single catalyst in the presence of a lithium amide base (LiHMDS) in NMP as solvent. The developed protocol tolerates several key functions, and can be applied to both aryl and alkynes.

## Experimental Section

**General method A.** In a 12 mL screw-cap vial,  $\text{FeCl}_2$  (6.3 mg, 0.05 mmol) in NMP (1.0 mL) was treated with LiHMDS solution (0.75 mL, 1.0 M in THF, 1.5 equiv.).

The reaction mixture was allowed to stir until the disappearance of the solid (5-7 min), then the vial was put in a freezer for 15-20 min. Iodoalkane (1.0 mmol, 2.0 equiv.) was added at once followed by the alkyne (0.5 mmol, 1.0 equiv.). The reaction mixture was allowed to stir

for 17h at ambient temperature, then quenched with water. The aqueous phase was extracted 3 times with MTBE and the combined extracts were washed 3 times with water, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude product was purified by column chromatography (SiO<sub>2</sub>, 0-5% EtOAc in petroleum ether).

**General method B.** FeCl<sub>2</sub> (6.3 mg, 0.050 mmol, 10 mol%) was stirred with LiHMDS (1.0M solution in THF, 0.15 mL, 0.15 mmol, 30 mol%) in 1.0 mL of NMP in a vial until all the solid was dissolved. The resulting clear yellowish solution was transferred to a 50 mL Schlenk flask with the magnetic stirring bar using 0.3 mL NMP for the washing. The flask was sealed with a silicon septum and removed from the glove box to be connected to an Ar-flushed Schlenk manifold. The flask was allowed to cool down to 0 °C in an ice bath. A solution of alkyne (1.0 mmol, 2.0 equiv.) and iodoalkane (0.50 mmol, 1.0 equiv.) in 0.7 mL of NMP was carefully transferred to the flask under vigorous stirring over 10 min followed by 50 µL of LiHMDS solution (1.0 M in THF). The resulting mixture was allowed to stir for 20 min at 0 °C. LiHMDS solution was then added in small portions every 10 min (7x50 µL then 5x100 µL, for a total amount of 0.9 mL, 0.9 mmol, 1.8 equiv.). The reaction mixture was then allowed to gradually warm to room temperature in the ice bath and stirred overnight at r.t. The next day it was quenched with water and MTBE. The aqueous phase was extracted 3 times with MTBE and the combined organic extracts were washed 3 times with water, dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed in vacuo. The crude product was purified by column chromatography (SiO<sub>2</sub>, petroleum ether + 1% triethylamine, 0% to 5% EtOAc).

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