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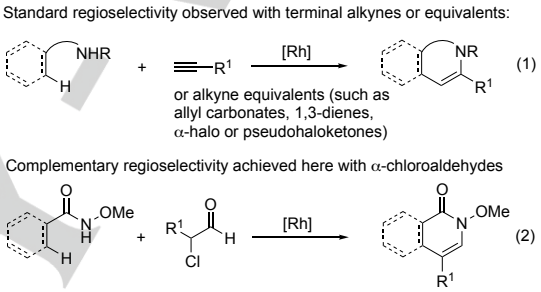
Microwave-Assisted Synthesis of Heterocycles by Rh(III)-Catalyzed Annulation of *N*-Methoxyamides with α-Chloro-aldehydes

Ji-Rong Huang and Carsten Bolm*

Abstract: α-Chloroaldehydes have been used as alkyne equivalents in rhodium-catalyzed syntheses of isoquinolones and 3,4-dihydroisoquinolins starting from *N*-methoxyamides. Compared to the existing technology, a complementary regioselectivity is achieved. Mechanistic investigations have been performed, and it was found that steric effects of both substrate and additive determine the product selectivity. Various other heterocycles such as isoquinolines and lactones can be prepared via the products.

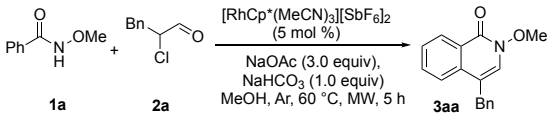
In recent years, transition metal-catalyzed oxidative annulation has emerged as a viable tool for the assembly of heterocycles.[1] Rhodium complexes, which exhibit high efficiency in C–H bond activations, have been recognized as effective catalysts for diverse transformations. Among them, annulations with alkynes represent a practical approach for the synthesis of pharmacologically important heterocycles.[2] The regioselective insertion of unsymmetrical internal alkynes, however, has remained a challenge in such reactions as it is largely determined by the inherent electronic and steric factors of the substrates. To reverse the intrinsic regioselectivity, tether-mediated intramolecular cyclizations have been introduced.[3a] Alternatively, 2-acetylenic ketones with weakly coordinated carbonyl groups could be applied.[3b] As internal alkyne equivalents, diazo compounds led to annulated heterocycles with specific regio-selectivities.[4] In general, annulations with terminal alkynes proved difficult due to competing alkyne dimerizations (Glaser coupling). To solve this restraint, Guimond et al. developed a rhodium-catalyzed redox-neutral synthesis of isoquinolones.[5] The exclusive regioselectivity of the insertion was achieved by a substitution at the 3-position. Furthermore, allyl carbonates[6a-d] and 1,3-dienes[6e] have been utilized as equivalents of terminal alkynes. Recently, Glorius and co-workers introduced the $C(_{Sp}{}^3)$-based electrophiles α-halo or pseudohaloketones as equivalents of preoxidized terminal alkynes.[7a] Subsequently, others utilized such formal S_N-type reactions for constructing different heterocycles.[7b-d] In each case a pronounced regioselectivity was observed leading to products with the substituent located next to the nitrogen directing group [Scheme 1, Eq. (1)].[8] After analyzing mechanistic details we hypothesized that using α-chloroaldehydes could reverse the regioselectivity. However, a number of challenges had to be addressed with α-chloroaldehydes as coupling partners: First, aldehyde C–H bonds were known to be reactive towards transition metals,[9] which could lead to deleterious reactions here. Second, α-chloroaldehydes had two electrophilic sites and both the chloro and the carbonyl group could compete in reactions with an intermediately formed nucleophilic rhodacycle resulting in product mixtures.[10] Third, compared to α-halo or pseudohaloketones, aldehydes exhibited a lower coordination ability with metal centers,[11] and forth, a rather sterically congested tertiary carbon center would result from the initially required formal S_N-type substitution (of the chloro group).[12] The overcoming of these issues and the success of our approach is presented here [Scheme 1, Eq. (2)].



Scheme 1. Rhodium-catalyzed annulations with alkynes and equivalents thereof.

The annulation studies were initiated by taking *N*-methoxy-benzamide (**1a**) and 2-chloro-3-phenylpropanal (**2a**) as starting materials, which we expected to result in heterocycle **3aa** (Table 1). After an extensive screening (see Supporting Information), a microwave-assisted coupling catalyzed by $[RhCp^*(MeCN)_3][SbF_6]_2$ in the presence of NaOAc and $NaHCO_3$ was found to be optimal leading to **3aa** in 72% yield after 5 h (Table 1, entry 1). The heating mode largely affected the reaction outcome, as revealed by a

Table 1. Screening of the reaction conditions.[a]



1a **2a** **3aa**

Entry	Variable	Yield [%][b]
1	-	72
2	Use of a preheated oil bath for 60 h	65
3	Reaction time of 3 h	58
4	Reaction time of 3 h at 100 °C	49
5	Use of Cs_2CO_3 instead of $NaHCO_3$	38
6	Use of K_3PO_4 instead of $NaHCO_3$	57
7	Use of TEA instead of $NaHCO_3$	56
8	Use of 1.5 equiv of NaOAc	47
9	Use of 0.5 equiv of $NaHCO_3$	55
10	Use of 2.0 equiv of $NaHCO_3$	76

[a] A mixture of **1a** (30.2 mg, 0.2 mmol), **2a** (100.8 mg, 0.6 mmol), $[RhCp^*(MeCN)_3][SbF_6]_2$ (8.1 mg, 5 mol %), NaOAc (49.2 mg, 3.0 equiv) and $NaHCO_3$ (16.8 mg, 1.0 equiv) in dry MeOH (1.0 mL) was stirred under Ar at 60 °C for 5 h under microwave irradiation. [b] After column chromatography.

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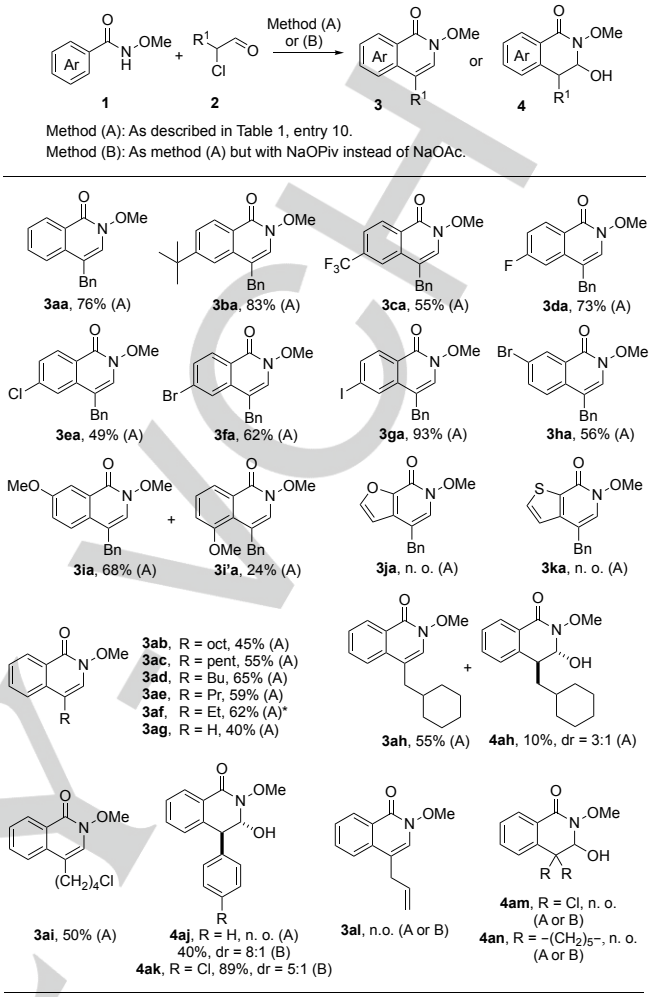
catalysis performed in a preheated oil bath, which provided **3aa** in only 65% yield after 60 h (Table 1, entry 2). Thus, microwave irradiation was applied when the effects of time, temperature, and additives were evaluated (Table 1, entries 3-10). As a result, the yield of **3aa** could be improved to 76% by increasing the amount of $NaHCO_3$ from the commonly used 1 equiv to 2 equiv (Table 1, entry 10).

Under the optimized conditions, the scope of the cross coupling was explored (Schemes 2 and 3). First, the *N*-methoxybenzamide structure was varied. 2-Chloro-3-phenylpropanal (**2a**) was kept as coupling partner. In general, para-substituted *N*-methoxybenzamides reacted well providing 4-substituted *N*-methoxyisoquinolones (**3aa**-**3ga**) in moderate to good yields. With benzamide **1h** having a bromo substituent in the meta position of the arene, only **3ha** was obtained as exclusive product in 56% yield. In contrast, starting from compound **1i** with the same molecular scaffold but bearing a *meta*-methoxy group gave a mixture of isomeric isoquinolones **3ia** and **3i'a** in yields of 68% and 24%, respectively. *N*-Methoxyisoquinolones **3ja** and **3ka** remained inaccessible presumably due to formation of unreactive chelates of rhodium intermediates with the heterocylic cores of the furanyl- and thiophenyl-based starting materials. An entirely different reaction behavior was observed with *ortho*-substituted *N*-methoxybenzamides, and those results will be presented in Scheme 3.

The substrate scope was further evaluated by studying couplings between various 2-chloroaldehydes and *N*-methoxybenzamide **1a**. Unbranched alkyl-substituted substrates afforded isoquinolones **3ab**-**3af** and **3ai** in yields ranging from 45% to 65% (Scheme 2). Commercial available 2-chloroacetaldehyde (50 wt % in water) could directly be applied (in the presence of MS 4 Å) leading to **3ag** in 40% yield. An unexpected observation was made in the reaction of **1a** with 2-chloro-3-cyclohexyl propanal (**2h**). Besides *N*-methoxyisoquinolone **3ah** (55% yield), 3,4-dihydroisoquinolin **4ah** was isolated in 10% yield (as a 3:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy). The latter product type was also observed in couplings of 2-aryl-substituted 2-chloroaldehydes. Those substrates, however, did not react under the standard reaction conditions (Method A), but required changing the base from NaOAc to NaOPiv (Method B). Accordingly, **4aj** and **4ak** were accessed in yields of 40% and 89% yield, respectively. The diastereomeric ratios were 8:1 (for **4aj**) and 5:1 (for **4ak**). The structure of **4aj** was further confirmed by methylation of the hydroxyl group. The attempt to prepare **3al** from **1a** and 2-chloropent-4-enal (**2l**) failed, presumably due to coordination tendency of the terminal double bond of the aldehyde. Also **4am** and **4an** remained inaccessible [from chloral (**2m**) and 2-chloro-2-cyclohexylethanal (**2n**), respectively] revealing that the presence of an α-hydrogen at the aldehyde was critical for the catalysis to occur.

As mentioned above, the reaction behavior of *ortho*-substituted *N*-methoxybenzamides differed from the one observed with substrates having other substitution patterns (which, for example, led to **3aa**-**ha**). This was first found in the attempt to couple *ortho*-iodo *N*-methoxybenzamide **1l** with 2-chloro-3-phenylpropanal (**2a**) which, to our suprise, did not proceed under the aforementioned standard reactions conditions (method A, with NaOAc as base). However, as observed in the aldehyde variation study, a reaction occurred when NaOPiv was used instead of NaOAc (method B). Also in this case, the product was not the initially expected isoquinolone, but



Scheme 2. Scope of the rhodium-catalyzed annulations (part 1); n.o. = not observed; * use of 0.4 mmol of **1a** and 0.2 mmol of **2f**.

3,4-dihydroisoquinolin **4la**, which was isolated in 86% yield as an 8:1 mixture of diastereomers (Scheme 3). Other *ortho*-substituted benzamides reacted analogously, and the yields of the corresponding 3,4-dihydroisoquinolins were high (reaching 96% for *ortho*-bromo-substituted **4na**; Scheme 3). A few observations shall be highlighted: First, scaling-up the catalysis towards **4ma** proceeded well, and on a 2 mmol scale, the product was obtained in 88% yield.[13] Second, initially, an unprotected phenolic substrate was used for the synthesis of **4qa**. Although the coupling occurred, the yield was low (20%). Using the *O*-acetyl-protected *N*-methoxybenzamide (**1r**) proved beneficial leading to 45% of **4qa** with a dr of 15:1 after direct hydrolysis. Third, applying method A in the coupling of 2-methoxy *N*-methoxybenzamide **1s** with **2a** gave a 1:1 mixture of isoquinolone **4sa** and 3,4-dihydroisoquinolin **3sa** (as determined by ^{1}H NMR spectroscopy). Following method B, led to **4sa** exclusively (in 77% yield). Testing the sodium salt of N-Boc leucine in this coupling (instead of NaOAc or NaOPiv, method C) gave 86% of a 2:1 mixture of **4sa** and **3sa**, which was separated by preparative TLC. Finally, also couplings of **2a** with 2,4-disubstituted *N*-methoxy benzamides afforded mixtures of the corresponding 3,4-dihydroisoquinolins (**4ta** and **4ua**) and isoquinolones (**3ta** and **3ua**). Testing

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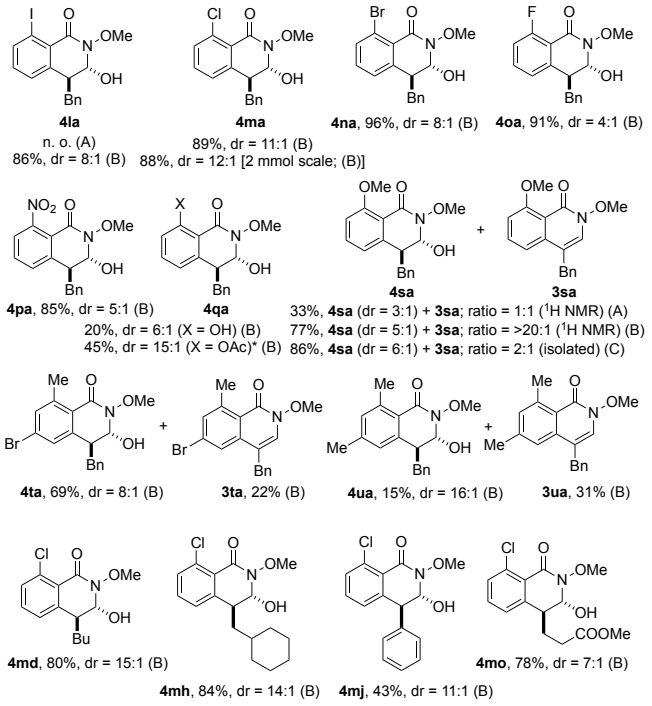
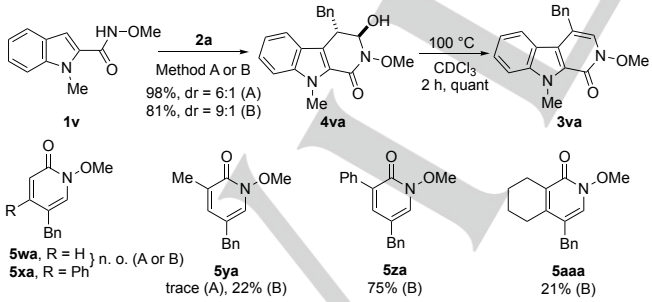


Scheme 3. Scope of the rhodium-catalyzed annulations (part 2); methods (A) and (B) as described in Scheme 2; method (C): as method (A), but with the sodium salt of *N*-Boc-Leu instead of NaOAc; n.o. = not observed; * use of 2-(methoxycarbamoyl)phenyl acetate (**1r**); after work-up **4qa** with X = OH was isolated.

other α-chloro aldehydes (than **2a**) in reactions with 2-chloro-*N*-methoxybenzamide (**1m**) gave 3,4-dihydroisoquinolins **4md**, **4mh**, **4mj**, and **4mo** as the only products in yields ranging from 43% to 84%.

To further expand the substrate scope, indole-2-carboxamide (**1v**) was applied (Scheme 4). Reacting **1v** with **2a** gave **4va** in yields of 98% (dr = 6:1) and 81% (dr = 9:1) following method A and method B, respectively. Heating of **4va** in $CDCl_3$ to 100 °C for 2 h led quantitatively to **3va**.

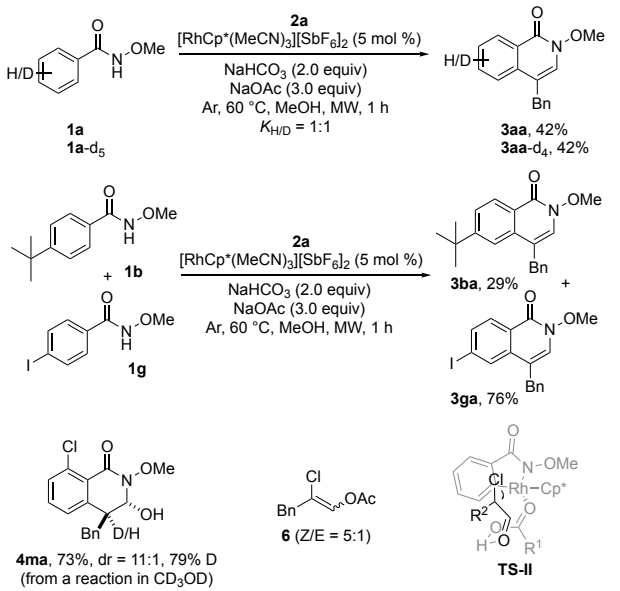


Scheme 4. Couplings of **2a** with indole-2-carboxamide (**1v**) and *N*-methoxy-acrylamides.

Next, *N*-methoxyacrylamides were tested in reactions with **2a** (Scheme 4). To our disappointment, neither method A nor method B led to products **5wa** and **5xa**. In contrast, 2-pyridones **5ya**-**5aaa** derived from *N*-methoxyacrylamides with α-alkyl or α-phenyl substituents were obtained in yields of up to 75%. Thus, for product formation, the presence of a substituent at C2 was essential, and overall, method B proved superior over method A.[14]

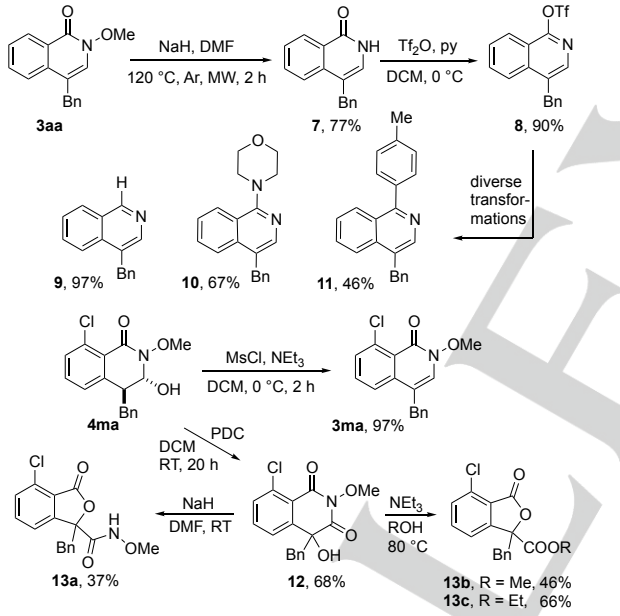
Further experiments were conducted to investigate mechanistic details (Scheme 5 and Supporting Information).[15] The kinetic isotope effect ($K_{H/D}$ = 1:1, after 1 h) observed in parallel reactions using *N*-methoxyamide **1a** and **1a**-d_5 indicated that the C−H cleavage was not rate-determining (Scheme 5, top). Intermolecular competition reaction between **2a** and substrates **1b** and **1g** revealed that the aryl moiety with lower electron density facilitated the C−H bond activation (Scheme 5, middle). Performing the coupling of **1m** and **2a** in CD_3OD (following method B) led to 73% of **4ma** (dr = 11:1) with 79% deuterium incorporation in the α-position of the benzyl group. This result suggested the involvement of an enolic intermediate in the process, which was further supported by the the coupling of **1m** with enantioenriched **2a** (79% ee), providing 84% of (essentially) racemic **4ma** (dr = 11:1, 1% ee). Finally, also enol acetate **6** (*Z*/*E* = 5:1) reacted with *N*-methoxyamide **1a** providing **3aa** in 64% yield (following method A).

As generally accepted, most coupling reactions proceed by direct coordination of both reaction partners at the metal center. Explaining the influence of the anions (OAc or OPiv) on both the product formation and the regioselectivity of the process has, however, remained difficult. Although the mechanistic details of the coupling reported here are still unclear, two scenarios involving the anions can be envisaged. In the first one, the combination of aldehyde and anion (OAc or OPiv) generates an ester enolate (such as enol acetate **6**), which then completes the coupling reaction by alkene insertion.[6] Alternatively, the protonated form of the anion acts as ligand assisting the approach of the aldehyde towards the rhodium species by hydrogen bonding interaction (**TS-II**) (see Supporting Information).[16] In any case, the steric factors induced by both the substrate and the anion (OAc or OPiv) will account for the product generation.



Scheme 5. Mechanistic investigations.

To demonstrate the synthetic value of the products, various functionalizations were studied (Scheme 6). The *N*-methoxy group of **3aa** was removed by treatment with NaH in DMF at 120 °C under microwave irradiation leading to benzolactam **7** in 77% yield. Upon reaction of **7** with triflic anhydride, **8** was obtained in 90% yield. The latter product proved useful for the synthesis of isoquinolines **9**-**11**, which were accessed by reductive deoxygenation and cross-couplings (for details see Supporting Information). 3,4-Dihydro-isoquinolin **4ma** could readily be converted into *N*-methoxy-benzamide **3ma** by treatment with a mixture of mesyl chloride and triethylamine. The ease of this dehydration providing the product in 97% yield after 2 h at 0 °C was unexpected because the starting material was stable at ambient conditions for weeks. Also surprising was the reaction of **4ma** with PDC, which led to **12** in 68% yield. Apparently, oxidation had occurred at two positions, the hydroxyl group and the benzylic C–H.[17] Product **12** proved valuable because under basic conditions, lactones **13a**-**c** were formed. While the first product resulted from deprotonation of the hydroxyl group followed by intramolecular carbonyl addition, lactones **13b** and **13c** were obtained by the aforementioned process and a subsequent inter-molecular esterification with MeOH or EtOH, respectively.



Scheme 6. Product derivatizations.

In conclusion, α-chloroaldehydes have been used as equivalents of terminal alkynes allowing to access isoquinolones and 2-pyridones with complementary regioselectivity compared to known processes. With sterically crowded amides or aldehydes, 3,4-dihydroisoquinolins are formed as sole products. Presumably the added sodium salt participates in the reaction by generating an ester enolate species or by acting as ligand stabilizing the association of the aldehyde to the metal by hydrogen bonding interactions. Finally, both isoquinolones and 3,4-dihydroisoquinolins were converted to other molecular scaffolds demonstrating their synthetic value.

Acknowledgements

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Keywords: rhodium catalysis • α-chloroaldehyde • hydrogen bonding • isoquinolone

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[12] For the only example of a formal S_N-type substitution involving an α-halo or pseudohaloketone forming a tertiary carbon center, see ref. 7c.

[13] The couplings of **1a** with **2a** and **1m** with **2a** were also performed on a gram scale (6 mmol). Because of the size restrictions of the microwave reactor, those reactions were carried out using an oil bath for the heating (to 60 °C in MeOH). Additional changes referred to the amount of **2a**, which was reduced to 2 equiv instead of the commonly applied 3 equiv., and the catalyst loading, which was changed from 5 mol % to 2.5 mol %. In contrast to the microwave-assited catalyses, extended reaction times were required for achieving high conversions. Finally, with $NaHCO_3$ (2 equiv) and NaOAc (3 equiv) the reaction of **1a** with **2a** led to a mixture of 57% of **3aa** and 16% of 3,4-dihydroisoquinolin **4aa** (dr = 17:1) after 48 h. Analogously, but with NaOPiv instead of NaOAc, the coupling of **1m** with **2a** gave 82% of **4ma** (dr = 7:1) after 20 h.

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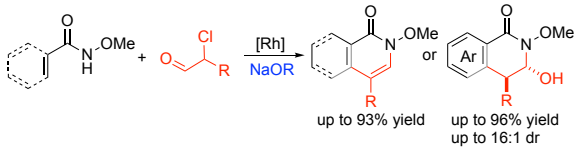

α-Chloroaldehydes are used as equivalents of terminal alkynes allowing to prepare isoquinolone, 2-pyridone and 3,4-dihydroisoquinolins with complementary regio-selectivity to known processes. Such products proved valuable for approaching other heterocycles. The anion of an added sodium salt has a great impact on the formation of the products, presumably by supporting an ester enolate generation or stabilizing assemblies induced by hydrogen bond interactions.

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