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Nickel-Catalyzed Claisen Condensation Reaction between Two Different Amides

Jiajia Chen, Man Xu, Subeen Yu, Yuanzhi Xia,* and Sunwoo Lee*

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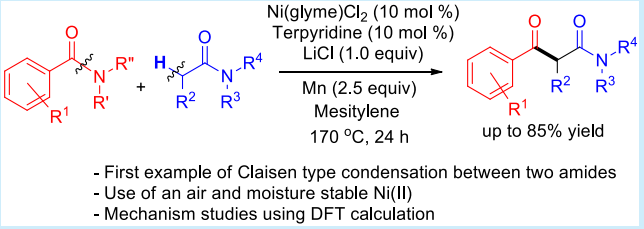
ABSTRACT: A nickel-catalyzed Claisen condensation reaction between two amides, where one possesses an α-proton, for the synthesis of β-ketoamides was developed. Ni(glyme)Cl_2 and terpyridine serve as the active catalysts in the presence of Mn and LiCl. *N*,*N*-Methylphenyl and *N*,*N*-diphenyl benzamide derivatives react with cyclic and noncyclic amides to give their corresponding β-ketoamides in moderate to good yields. In addition, a DFT calculation suggests that reductive elimination is the rate-determining step.



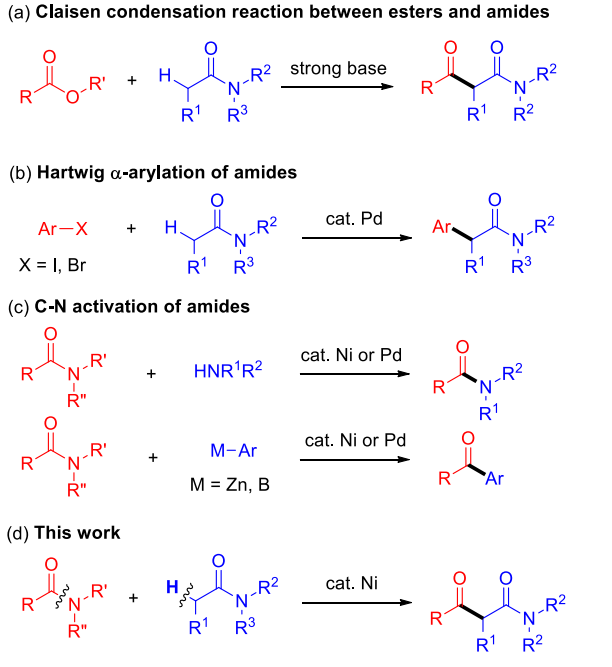
Most of the materials we use on a regular basis are polymers and consist of long carbon chains. The Claisen condensation reaction, first reported in 1881, is one of the most classical reactions used for formation of carbon−carbon bonds.[1] This reaction occurs between an ester and another carbonyl compound containing an α-proton in the presence of a base to afford a β-keto carbonyl compound. β-Keto carbonyl functionality has been widely employed in further transformations and is found in many valuable organic molecules.[2]

In particular, β-ketoamides are useful building blocks found in bioactive molecules.[3] The Claisen condensation reaction between an ester and an amide has frequently been employed as a useful tool for the construction of a β-ketoamide backbone (Scheme 1a).[4] However, this approach requires harsh reaction conditions, such as a strong base and low temperatures, because the α-proton of an amide is much less acidic than that of other carbonyl compounds such as esters and ketones, which leads to poor functional group compatibility.

Transition-metal-catalyzed carbon−carbon bond forming reactions are attractive because they can be carried out under mild conditions. Hartwig and Buchwald independently developed the palladium-catalyzed coupling reaction between aryl halides and the α-carbon atom in carbonyl compounds such as ketones,[5] and esters.[6] Hartwig demonstrated that the α-carbon of an amide can be activated under mild reaction conditions and shows good functional group tolerance in the carbon−carbon bond forming process (Scheme 1b).[7]

Recently, activation of the C−N bond in an amide using transition metal catalysis has received attention because the reaction may be useful for synthesizing other carbonyl compounds.[8] The reaction between an amide and an amine affords a new amide via transamidation.[9] Nickel-catalyzed transamidation of an amide with an alcohol provides the corresponding ester.[10] Furthermore, a ketone is formed when an amide is allowed to react with carbon nucleophiles such as aryl boronic acid derivatives in the presence of a nickel catalyst

Scheme 1. Condensation and Coupling Reactions of Amide



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(Scheme 1c).[11] However, there are no examples of the reaction utilizing the α-carbon of carbonyl compounds.

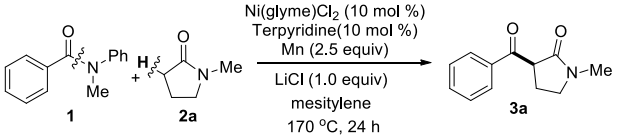
To the best of our knowledge, Claisen condensation reactions between two different amides have not been reported to date, although the transition-metal-catalyzed α-arylations of amides and transamidation reactions have. The development of Claisen condensation between two amides is challenging because of the high stability of the C−N bond and low activity of the α-proton of the amide. To overcome this challenge, we employed a nickel-based catalytic system. Here, we report for the first time the nickel-catalyzed coupling reaction of the acyl group of an amide and α-carbon of another amide for the synthesis of β-ketoamides (Scheme 1d).

N-Methyl-*N*-phenylbenzamide and *N*-methylpyrrolidin-2-one (NMP) were chosen as model substrates to identify the optimal conditions for the coupling reaction (Table 1).

After extensive screening of the reaction parameters, we established that Ni(glyme)Cl_2 and terpyridine in mesitylene afforded the desired product **3a** in 81% yield in the presence of Mn and LiCl at 170 °C (entry 1). The impact of several reaction parameters is summarized in Table 1. Reactions performed in the absence of Ni(glyme)Cl_2, terpyridine, Mn, and LiCl either did not afford the desired product or resulted in exceedingly low yields of the product (entries 2−5). Reactions carried out using $NiCl_2$ and $Ni(OAc)_2$ afforded **3a** in 41% and 30% yields, respectively (entries 6 and 7). Bipyridine gave a higher product yield than other nitrogen-based ligands including PMDETA and 4,7-Me_2Phen (entries 8−10). Reactions using phosphine ligands such as Xantphos, dppb, PPh_3, and PCy_3 provided **3a** in 54%, 47%, 69%, and 27% yields, respectively (entries 11−14). The reactions performed using LiI instead of LiCl gave the desired product in 44% yield. However, other salts such as $LiBF_4$ and KCl did not lead to the desired product (entries 15−17). In addition, the yield of the desired product decreased to 23% when the amount of LiCl was reduced to 0.5 equiv (entry 18). The use of diglyme as a solvent led to a poor product yield (entry 19). When the amount of catalyst or Mn was reduced, the product yields decreased (entries 20−22). The reaction at 150 °C gave an inferior product yield (entry 23). Unfortunately, the reaction at low temperature (50 °C) did not give the desired product (entry 24).

After establishing optimal conditions, we proceeded to evaluate the substrate scope of the reaction. To this end, we used a variety of tertiary amides in reaction with NMP (Table 2).

Table 1. Optimal Conditions for the Nickel-Catalyzed Coupling Reaction between 1 and 2a[a]



entry	change from the standard conditions	yield (%)[b]
1	none	81
2	no Ni(glyme)Cl_2	trace
3	no terpyridine	8
4	no Mn	0
5	no LiCl	0
6	$NiCl_2$ instead of Ni(glyme)Cl_2	41
7	$Ni(OAc)_2$ instead of Ni(glyme)Cl_2	30
8	bipyridine instead of terpyridine	70
9	PMDETA instead of terpyridine	56
10	4,7-Me_2Phen instead of terpyridine	21
11	Xantphos instead of terpyridine	54
12	dppb instead of terpyridine	47
13	PPh_3 (20 mol %) instead of terpyridine	69
14	PCy_3 (20 mol %) instead of terpyridine	27
15	LiI instead of LiCl	44
16	$LiBF_4$ instead of LiCl	0
17	KCl instead of LiCl	0
18	0.5 equiv of LiCl instead of 1.0 equiv	23
19	diglyme instead of mesitylene	29
20	5 mol % Ni and L instead of 10 mol %	62
21	1.0 equiv of Mn instead of 2.5 equiv	30
22	0.5 equiv of Mn instead of 2.5 equiv	3
23	150 °C instead of 170 °C	66
24	50 °C instead of 170 °C	0

[a]Reaction conditions are as follows: **1** (0.3 mmol), **2a** (1.5 mmol), Ni(glyme)Cl_2 (0.03 mmol), terpyridine (0.03 mmol), Mn (0.75 mmol), and LiCl (0.3 mmol) were reacted in mesitylene (0.4 mL) at 170 °C for 24 h. [b]Yields are isolated.

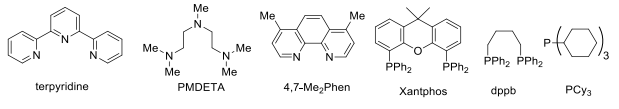
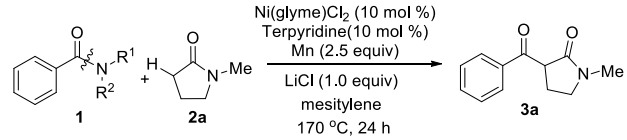


Table 2. Reaction of 2a with a Variety of Benzamide[a]



entry	-NR^1R^2	yield (%)[b]	entry	-NR^1R^2	yield (%)[b]
1		78	4		20
2		28	5		25
3		22	6		0

[a]Reaction conditions: **1** (0.3 mmol), **2a** (1.5 mmol), Ni(glyme)Cl_2 (0.03 mmol), terpyridine (0.03 mmol), Mn (0.75 mmol), and LiCl (0.3 mmol) were reacted in mesitylene (0.4 mL) at 170 °C for 24 h. [b]Isolated yield.

The reaction with *N*,*N*-diphenylbenzamide provided **3a** in a similar yield to that observed with *N*,*N*-diphenylbenzamides (entry 1). However, *N*-ethyl-*N*-phenylbenzamide, *N*-benzyl-*N*-phenylbenzamide, and *N*,*N*-dimethylbenzamide afforded **3a** in poor yields (entries 2−4). Interestingly, *N*-phenylbenzamide, a secondary amide, reacted with NMP to give **3a** in 25% yield (entry 5), while activated amides such as *N*-phenyl-*N*-tosylbenzamide did not give the desired product (entry 6). Based on these results, we confirmed that *N*-methyl-*N*-phenylbenzamide and *N*,*N*-diphenylbenzamide are suitable activated amides for the nickel-catalyzed Claisen condensation with NMP.

Next, we evaluated a variety of *N*-methyl-*N*-phenylbenzamides and *N*,*N*-diphenylbenzamides bearing a substituent at the benzoyl group for reaction with NMP under the optimal conditions (Scheme 2). Benzamides with an alkyl substituent at the meta- or para-position afforded the corresponding β-ketoamides in good yields. However, 4-

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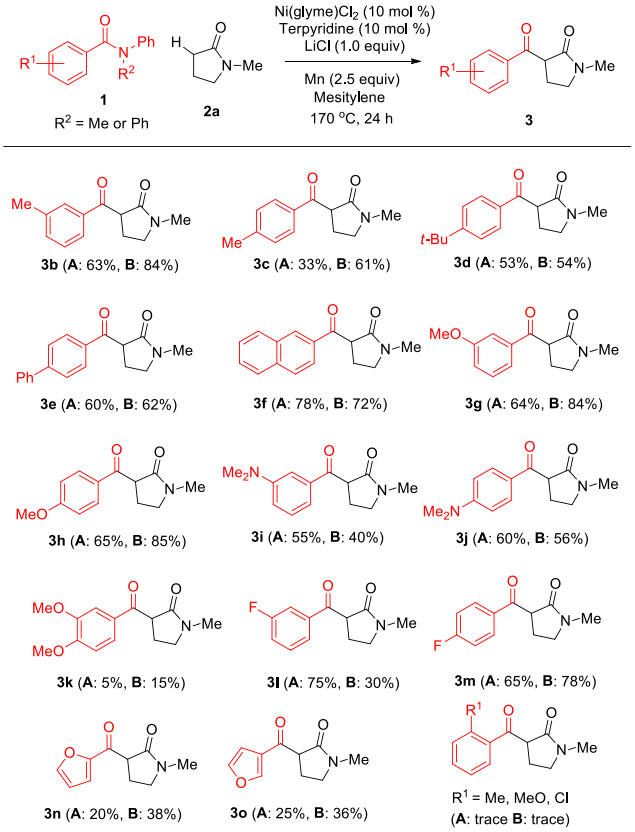
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Claisen Condensation Reaction between Benzamides and NMP[a]

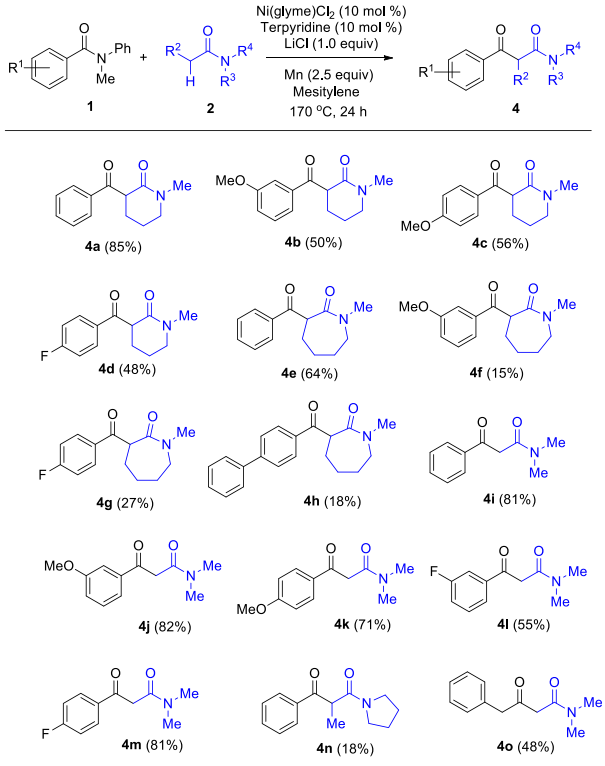


[a]Reaction conditions: **1** (1.0 mmol), **2a** (5.0 mmol), Ni(glyme)Cl_2 (0.1 mmol), terpyridine (0.1 mmol), Mn (2.5 mmol), and LiCl (1.0 mmol) were reacted in mesitylene (2.0 mL) at 170 °C for 24 h. The numbers in the parentheses are isolated yields. **A** is yield obtained from *N*-methyl-*N*-phenylbenzamide, and **B** is yield obtained from *N*,*N*-diphenylbenzamide.

methyl-*N*-methyl-*N*-phenylbenzamide provided **3c** in only 33% yield. 1,1-Biphenyl and 1-naphthyl amides gave **3e** and **3f** in good yield. Methoxy- and *N*,*N*-dimethylamino-substituted benzamides gave their corresponding products **3g**, **3h**, **3i**, and **3j**, in moderate to good yields. However, dimethoxy-substituted benzamides gave **3k** in low yield for both **A** and **B**. Benzamides bearing a fluorine group at the *meta*- or *para*-position gave **3l** and **3m** in moderate to good yields. 2- and 3-Furamide derivatives afforded the desired products **3n** and **3o**, albeit in low yields. Unfortunately, benzamides bearing an *ortho*-substituent afforded only trace amounts of the desired product.

We then attempted to expand the scope of the amides bearing an α-hydrogen in the reaction using a variety of *N*-methyl-*N*-phenyl benzamides derivatives (Scheme 3). We employed 1-methylpiperidin-2-one instead of NMP and reacted it with a variety of benzamide derivatives to afford the desired β-ketoamides in 48% to 85% yields. When 1-methylazepan-2-one was reacted with benzamide derivatives, we obtained the desired product **4e** in 64% yield in the case of *N*-methyl-*N*-phenyl benzamide. In contrast, substituted *N*-methyl-*N*-phenyl benzamides gave the products **4f**, **4g**, and **4h** in low yield. A noncyclic amide, *N*,*N*-dimethylacetamide, was also employed in the reaction with the *N*-methyl-*N*-phenyl benzamide derivatives and gave the desired product in good

Scheme 3. Claisen Condensation Reaction between *N*-Methyl-*N*-phenyl Benzamide and a Variety of Amides[a]

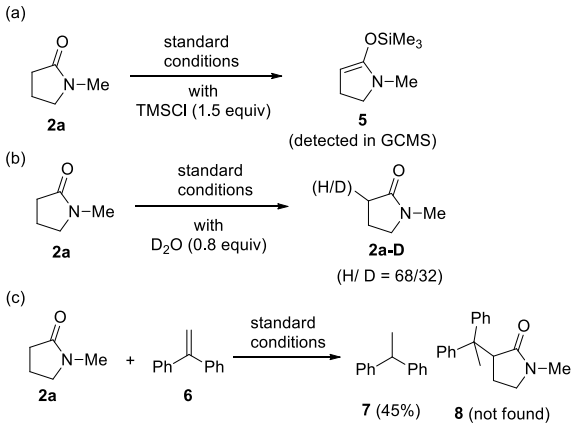


[a]Reaction conditions: **1** (1.0 mmol), **2** (5.0 mmol), Ni(glyme)Cl_2 (0.1 mmol), terpyridine (0.1 mmol), Mn (2.5 mmol), and LiCl (1.0 mmol) were reacted in mesitylene (2.0 mL) at 170 °C for 24 h. The numbers in parentheses are isolated yields.

yields. However, pyrrolidinylpropan-1-one afforded **4n** in only 18% yield. Interestingly, *N*-methyl-*N*,2-diphenylacetamide reacted with *N*,*N*-dimethylacetamide to afford **4o** in 48% yield.

We ran control experiments to gain insight into the reaction mechanism (Scheme 4).

Scheme 4. Control Experiments



When NMP was treated with TMSCl under standard conditions in the absence of benzamide, silyl enolate **5** was detected by GCMS analysis. In addition, when NMP reacted with D_2O under standard conditions, 32% deuteration occurred at the α-carbon of NMP. The reaction with NMP in the presence of 1,1-diphenylethylene, a radical trapping

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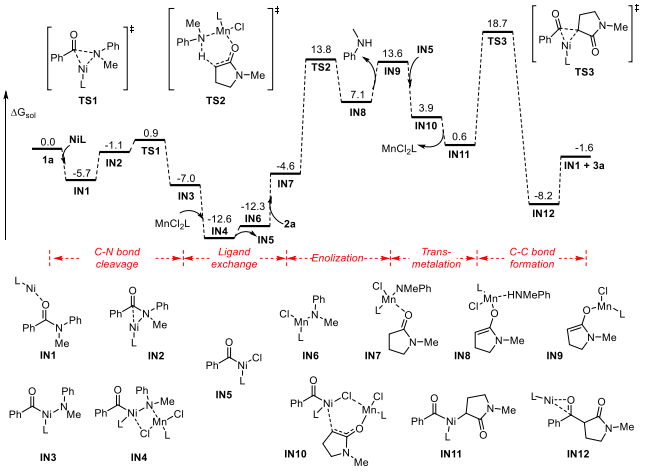
Org. Lett. XXXX, XXX, XXX−XXX

reagent, did not provide any trapping product but gave the hydrogenation product 1,1-diphenylethane.[12] These results indicate the reaction occurs via an ionic mechanism, with the formation of hydrogen.

To better understand the transformation, we did DFT calculations using **1a** and **2a** as model reactants to investigate the detailed mechanism (Scheme 5).[13,14] According to the

Scheme 5. Computed Potential Energy Surface for the Ni-Catalyzed Condensation between 1a and 2a (L = TPY; Relative Gibbs Free Energies in Solution Are in kcal/mol)



reaction conditions, LNi(0) should be formed as an active catalyst for the C−N bond cleavage of **1a** by first formation of complexes **IN1** and **IN2**. Calculations found that the oxidative addition of **1a** with LNi(0) is very facile via **TS1** with a very small barrier of 2.0 kcal/mol from **IN2**. Once **IN3** is formed, it complexes with $MnCl_2L$, generated in the reduction process of Ni(II). The reaction is exergonic by 5.6 kcal/mol to form **IN4**, which readily forms **IN5** and **IN6** by dissociation. The Mn(II) complex **IN6** is responsible for the enolization of **2a**. This step is difficult with Ni or other forms of Mn (see SI for details). From complex **IN7**, the alpha deprotonation of **2a** occurs via **TS2** with the assistance of the amino group. This step has a barrier of 18.4 kcal/mol and forms intermediate **IN8**.[15,16] Dissociation of *N*-methylaniline from **IN8** forms **IN9** endergonically. To undergo the transmetalation, **IN9** would complex with **IN5** to form **IN10**, which then generates **IN11** slightly exergonically and regenerates $MnCl_2L$ concurrently. The last step of C−C formation occurs via reductive elimination via **TS3**. This transition state has the highest relative free energy and is 31.3 kcal/mol above the local minimum **IN4**, suggesting that the reductive elimination should be the rate-determining step of the whole reaction. We also explored the alternative five-membered ring transition state involving enolate oxygen−nickel interaction; however, much higher energy was calculated due to the instability of the enolate intermediate with oxygen−nickel interaction. The effective combination of Ni and Mn was well supported by DFT results as much higher activation barriers if only one metal is used. The energy profiles for all unfavorable pathways are given in the Supporting Information.

In summary, we developed a nickel-catalyzed Claisen condensation of two different amides to furnish the desired *β*-ketoamides in the presence of manganese and LiCl. Among the electrophilic amides tested, we found *N*-methyl-*N*-phenyl benzamides and *N*,*N*-diphenyl benzamides to be effective substrates that gave good product yields. Cyclic amides having five-, six-, and seven-membered rings, *N*-methylpyrrolidin-2-one, 1-methylpiperidin-2-one, and 1-methylazepan-2-one, served as good nucleophiles that reacted with benzamide to produce the corresponding *β*-ketoamides in good yields. In addition, a noncyclic amide, *N*,*N*-dimethylacetamide, showed good activity for this reaction. Details of the transformation were provided by DFT calculations, which uncovered that the main steps include oxidative addition of Ni(0) to the C−N bond of the amide, formation of the manganese enolate, transmetalation, and reductive elimination. Among them, the reductive elimination step might be the rate-determining step. This is the first report of a metal-catalyzed Claisen condensation of two different amides. Future work in our lab will focus on further studies of the mild reaction conditions and expansion of the substrate scope.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00485.

Experimental procedures and spectral data for the products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Sunwoo Lee − *Department of Chemistry, Chonnam National University, Gwangju 61186, Republic of Korea;* orcid.org/0000-0001-5079-3860; Email: sunwoo@chonnam.ac.kr

Yuanzhi Xia − *College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, Zhejiang Province 325035, P. R. China;* orcid.org/0000-0003-2459-3296; Email: xyz@wzu.edu.cn

Authors

Jiajia Chen − *Department of Chemistry, Chonnam National University, Gwangju 61186, Republic of Korea; College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, Zhejiang Province 325035, P. R. China*

Man Xu − *College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, Zhejiang Province 325035, P. R. China*

Subeen Yu − *Department of Chemistry, Chonnam National University, Gwangju 61186, Republic of Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00485

Notes

The authors declare no competing financial interest.

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(13) DFT calculations were done by gas phase optimization and frequency calculation at the B3LYP/6-31G(d) (LANL2DZ for Ni and Mn) level of theory, and the solvation effects of mesitylene were

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Org. Lett. XXXX, XXX, XXX−XXX

evaluated with the M06/6-311+G(d,p) (SDD for Ni and Mn) method. The energies provided are relative free energies (in kcal/mol) corrected by solvation effects. More details are given in the Supporting Information for details.

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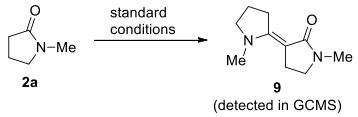

2a **9** (detected in GCMS)

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Org. Lett. XXXX, XXX, XXX−XXX