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Easy access to enamides: a mild nickel-catalysed alkene isomerization of allylamides†

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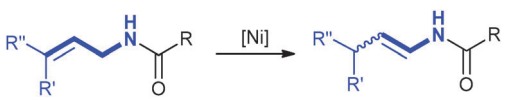
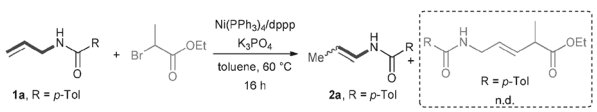
The first Ni-catalysed alkene isomerization of allylamides for the synthesis of enamides was demonstrated. Various substituted *N*-allylamides were found to be suitable substrates for this isomerization. Isotopic labelling experiments showed that it is an intramolecular hydrogen transfer process.

Enamides have proven to be extremely fascinating synthons due to their versatility for further synthetic transformations such as the Diels–Alder cycloaddition,[1] enamide–olefin ring-closing metathesis[2] and synthesis of important heterocycles.[3] Besides the above applications, this class of compounds has also been used in asymmetric hydrogenation reactions for the synthesis of enantioselectively pure amides.[4] Due to the importance of enamides, many efforts have been focused on their synthesis. The classic method is the direct acylation of imines with acyl chlorides or anhydrides.[5] However, this method suffers from the unstable and corrosive properties of the corresponding acylation reagents. Recently, a stoichiometric $TiCl_4$-promoted condensation of amides with aldehydes (or ketones) has also been developed for the synthesis of enamides.[6] For all of these transformations, by-products were generated in the reaction systems and stoichiometric amounts of bases were utilized. Consequently, developing novel processes for efficient and atom-economical assembling of enamides is highly desired. In this aspect, the direct alkene isomerization of allylamides is an atom-economic strategy to construct enamides.[7]



(1)

Many transition metal catalysts have been widely applied in alkene isomerization.[8] For the alkene isomerization of allylamides, the noble transition metal catalysts, such as Rh,[7c,9] Ru,[7c,9,10] Os[11] and Ir,[12] have mainly been used for the synthesis of enamides. However, only isolated examples have been reported with first-row transition metals as the catalysts for this transformation, in which toxic $Fe(CO)_x$[7a,9a,13] or $Cr(CO)_x$[14] complexes were applied. To the best of our knowledge, there has been no report on the use of nickel complexes as catalysts for the isomerization of allylamides to date. Herein, we report the first Ni-catalysed alkene isomerization of allylamides for the synthesis of enamides by using simple $Ni(PPh_3)_4$ as the catalyst under mild conditions [eqn (1)].



(2)

Recently, our group has reported a nickel-catalysed Heck-type alkenylation of α-carbonyl alkyl bromides with olefins.[15] When *N*-allyl-4-methylbenzamide (**1a**) was utilized as the substrate to react with ethyl 2-bromopropanoate, it was interesting to find that the alkene isomerization product **2a** was obtained in 36% yield [eqn (2)]. Following this initial discovery, we investigated a Ni-catalysed isomerization of allylamides for the synthesis of enamides.

As shown in eqn (2), ethyl 2-bromopropanoate was not involved in the alkene isomerization. Then, we tried to optimize the reaction conditions for this alkene isomerization using *N*-allyl-4-methylbenzamide (**1a**) as the model substrate. Interestingly, when $Ni(PPh_3)_4$ was solely applied as the catalyst in the absence of dppp (1,3-bis(diphenylphosphino)propane) and K_3PO_4, the product enamide **2a** was obtained in almost a quantitative amount at 60 °C. Furthermore, the reaction temperature could be lowered to 30 °C and a 99% GC yield was obtained (Table 1, entry 1). However, the reaction solution immediately turned green and finally no product was observed when the reaction mixture was exposed to oxygen or air (Table 1, entry 2). When $Ni(acac)_2$ was used as the catalyst precursor instead of

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† Electronic supplementary information (ESI) available: Characterization of all compounds and copies of ^1H and ^{13}C NMR spectra of isolated compounds. See DOI: 10.1039/c3cc43875a

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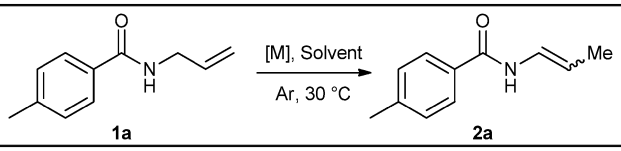
Table 1 Impacts of reaction parameters on the Ni-catalysed isomerization of *N*-ally-4-methylbenzamide[a]



1a 2a

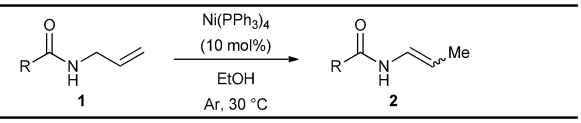
Entry	[M]	Solvent	Conversion	Yield[b] (%)
1	$Ni(PPh_3)_4$	Toluene	100	99 (94[d])
2[c]	$Ni(PPh_3)_4$	Toluene	—	—
3	$Ni(acac)_2$	Toluene	—	—
4	$Pd(PPh_3)_4$	Toluene	—	—
5	$FeCl_2$	Toluene	—	—
6	$CuCl_2$	Toluene	—	—
7	$Ni(PPh_3)_4$	THF	37	34
8	$Ni(PPh_3)_4$	DME	50	48
9	$Ni(PPh_3)_4$	EtOH	100	99 (99[d])
10	$Ni(PPh_3)_4$	MeOH	100	99

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.25 mmol), catalyst (0.025 mmol), solvent (2.0 mL), 30 °C, 9 h under an argon atmosphere. [b] Yield determined by GC analysis with biphenyl as the internal standard. [c] Under an air atmosphere. [d] Isolated yields.

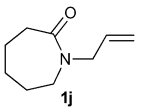
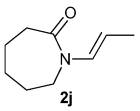
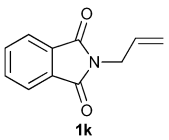
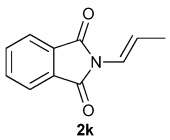
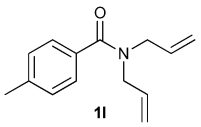
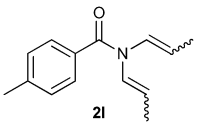
$Ni(PPh_3)_4$, substrate **1a** was almost quantitatively recovered (Table 1, entry 3), indicating that Ni(II) could not initiate the reaction. To further evaluate the superiority of the Ni catalyst for this allylamide isomerization, other transition metal catalyst precursors were tested. $Pd(PPh_3)_4$, $CuCl_2$ and $FeCl_2$ all showed no reactivity for the isomerization under the same conditions (Table 1, entries 4–6). Study of the solvent effects showed that the isomerization product could be obtained in THF or DME, but the yields decreased drastically (Table 1, entries 7 and 8). When a polar protic solvent was utilized, such as ethanol or methanol, the desired isomerization product was obtained in 99% yield, respectively (Table 1, entries 9 and 10). It was worth noting that the reaction could even be performed in industrial ethanol (95% of purity) to afford **2a** in an equivalent yield. Therefore, ethanol was chosen as the solvent. We have also tried 5 mol% and 1 mol% catalyst loadings, and the desired product **2a** was obtained in 99% and 78%, respectively, at 30 °C after 9 h. However, low catalyst loading sometimes has problematic generality and reproducibility for other substrates, therefore, catalyst with 10 mol% loading was applied as the general condition. The standard reaction conditions were determined to be: [$Ni(PPh_3)_4$] (10 mol%), ethanol, 30 °C, 9 h.

With the optimized conditions in hand, the isomerization reactions of a range of *N*-allylamides were tested (Table 2). First of all, feasibility of the *N*-protected groups was investigated. With both electron-donating and electron-withdrawing substituents on the aromatic rings, reactions proceeded smoothly to afford the desired products in excellent yields (Table 2, entries 1–4). Halide substituents could be well tolerated, which provided high potential for additional product functionalization (Table 2, entry 5). Moreover, *N*-alkyl protected allylamides such as *N*-phenylacetyl, *N*-pivaloyl and cyclic allylamide could also be well transformed into the corresponding isomerization products (Table 2, entries 6, 7 and 10). Notably, urea, carbamate and imide derivatives also afforded the isomerization product in moderate to excellent yields (Table 2, entries 8, 9 and 11).

Table 2 Substrate scope for the Ni-catalyzed isomerization of *N*-allylamides[a]



1 2

Entry	Substrate	Product	Yield[b] (%) (*E*/*Z*)
1	**1a:** R = *p*-MeC_6H_4	**2a:** R = *p*-MeC_6H_4	99 (56/44)
2	**1b:** R = *o*-MeC_6H_4	**2b:** R = *o*-MeC_6H_4	99 (60/40)
3	**1c:** R = *p*-$OMeC_6H_4$	**2c:** R = *p*-$OMeC_6H_4$	99 (53/47)
4	**1d:** R = *p*-$CF_3C_6H_4$	**2d:** R = *p*-$CF_3C_6H_4$	99 (47/53)
5	**1e:** R = *p*-ClC_6H_4	**2e:** R = *p*-ClC_6H_4	99 (77/23)
6	**1f:** R = $C_6H_5CH_2$	**2f:** R = $C_6H_5CH_2$	98 (61/39)
7	**1g:** R = ^{t}Bu	**2g:** R = ^{t}Bu	93 (96/4)
8	**1h:** R = NPh_2	**2h:** R = NPh_2	91 (39/61)
9	**1i:** R = Boc	**2i:** R = Boc	94[c] (66/34)
10	 **1j**	 **2j**	87 (100/0)
11	 **1k**	 **2k**	47[d] (100/0)
12	 **1l**	 **2l**	94 (—)

[a] Reaction conditions: **1** (0.25 mmol), $Ni(PPh_3)_4$ (0.025 mmol), ethanol (2.0 mL) at 30 °C for 9 h under an argon atmosphere. [b] Isolated yields. [c] Methanol as the solvent, 60 °C, 5d. [d] Methanol as the solvent, 60 °C.

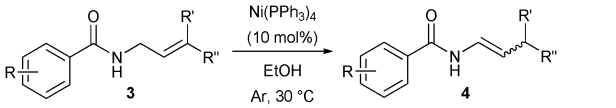
Isomerization of *N*,*N*-diallylamide could also generate *N*,*N*-di-(1-propenyl)amide (**2l**) in 94% yield (Table 2, entry 12).

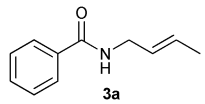
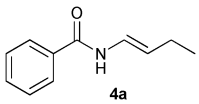
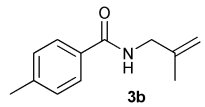
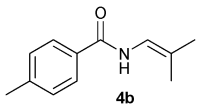
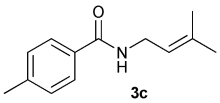
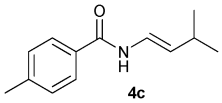
To further explore the substrate applicability of the reaction, *N*-allylamides with different allyl groups were also tested (Table 3). Substitutions at the allylic position could slow down the reaction rate of this isomerization. Therefore, prolonged reaction time and higher temperature were required to obtain excellent yields (Table 3, entries 1 and 2). A 1,1-disubstituted allylic system such as 4-methyl-*N*-(3-methylbut-2-enyl)benzamide worked well to afford the desired product **4c** in a moderate yield in 45 h at 60 °C (Table 3, entry 3).

It is noteworthy that the 'long-distance' migration of double bonds could be successfully achieved to generate the corresponding enimides. Homoallylamides, such as *N*-(but-3-enyl)-4-methylbenzamide **5a** afforded the isomerization product **6a** in 91% yield when the reaction time was prolonged to one week [Scheme 1, eqn (3)]. Isomerization of *N*-allylamide over 5 positions could also be realized [Scheme 1, eqn (4)], although a considerable amount of side-product resulting from the 'incomplete' double bond shift was obtained.

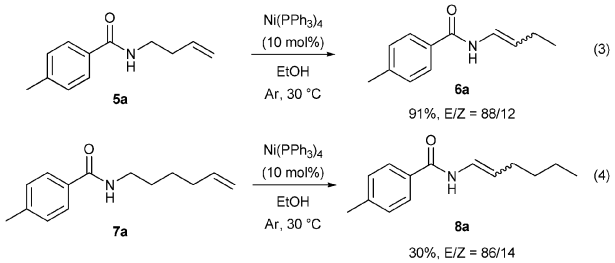
As this alkene isomerization could be conducted smoothly in a protonic solvent, we expected to know whether the solvent has participated in the transformation. Thus, deuteration experiments were performed as shown in Scheme 2. With CD_3OD as the reaction solvent, no deuterated product was obtained [Scheme 2, eqn (5)], while for the deuterated substances **1a**-*d* with the normal CH_3OH as the solvent, deuteration occurred wholly kept in the

Table 3 Substrate scope for the Ni-catalyzed isomerization of *N*-allylamides[a]

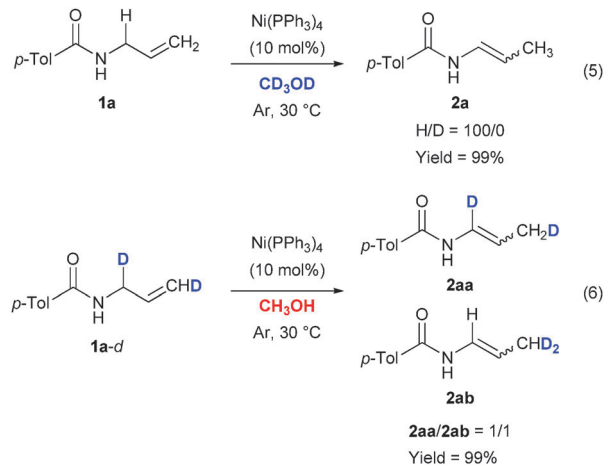


Entry	Substrate	Product	Yield[b] (%) (*E*/*Z*)
1			91[c] (100/0)
2			99[d]
3			50[e] (100/0)

[a] Reaction conditions: **3** (0.25 mmol), $Ni(PPh_3)_4$ (0.025 mmol), ethanol (2.0 mL) at 30 °C for 9 h under an argon atmosphere. [b] Isolated yields. [c] 7d. [d] 60 °C, 19 h. [e] 60 °C, 45 h.



Scheme 1 'Long-distance' migration of double bonds of *N*-allylamides.



Scheme 2 Deuteration experiments.

product molecules, and only the intramolecular hydrogen transfer product **2aa** and **2ab** were detected using GC-MS and NMR with a 1 : 1 ratio [Scheme 2, eqn (6)]. These results indicated that such a nickel-catalysed isomerization reaction underwent an intramolecular hydrogen transfer.

In conclusion, we have developed an inexpensive and convenient nickel-catalysed isomerization reaction of *N*-allylamides under mild conditions for the synthesis of enamides which were widely used in organic synthesis. Various substituted *N*-allylamides were found to be suitable substrates for this isomerization, and this method could also realise the 'long-distance' migration of double bonds. The reaction was performed well in industry grade alcohol. Studies on the scope of the reaction and mechanistic studies are underway.

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