Nickel-catalyzed [2 + 2 + 1] cycloaddition of alkynes, acrylates and isocyanates†

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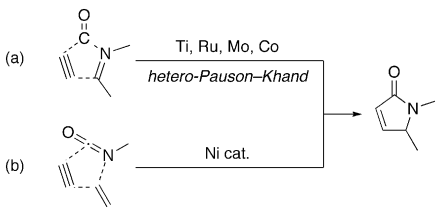
Intermolecular [2 + 2 + 1] cycloaddition which incorporates an alkyne, an isocyanate, and an alkene into a γ-butyrolactam proceeds with nickel catalyst.

Transition-metal-catalyzed cycloadditions are the most powerful methodologies for the construction of structurally diverse heterocyclic compounds from readily accessible starting materials.[1] A formal [2 + 2 + 1] cycloaddition, in which an alkyne, an imine and carbon monoxide are assembled, represents a facile synthetic access to structurally diverse γ-butyrolactams, and has been a research subject of great interest (Scheme 1a).[2,3] Herein, we wish to report an unprecedented type of [2 + 2 + 1] cycloaddition, which incorporates an alkyne, an isocyanate, and an alkene into a γ-butyrolactam by using nickel catalyst (Scheme 1b).

Our investigation began with an attempted [2 + 2 + 1] cycloaddition between 2-octyne (**1a**), methyl acrylate (**2a**), and phenyl isocyanate (**3a**). The results of optimization of reaction conditions are summarized in Table 1. We first examined ligands for the catalyst and found that a sterically hindered *N*-heterocyclic carbene ligand is effective for the cycloaddition to provide γ-butyrolactam **4aaa**. Phosphine ligands, such as PPh_3, PCy_3, and PMe_3, did not afford **4aaa** but gave 2-pyridone as a major product *via* [2 + 2 + 2] cycloaddition of two molecules of alkynes and an isocyanate (entries 1–3).[4,5] Among carbene ligands examined, IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) gave the best yield of **4aaa**.[6,7] Thus, the reaction of **1a**, **2a**, and **3a** in the presence of 10 mol% of $Ni(cod)_2$ and 10 mol% of IPr in 1,4-dioxane (100 °C) afforded γ-butyrolactam **4aaa** in 56% yield consisting of regioisomers in 5/1 ratio along with trace amount of 2-pyridone (*ca.* 5%) (entry 4). On screening of the molecular ratio of **1a**, **2a**, and **3a** to employ for the cycloaddition, it was found that the ratio of **1a**/**2a**/**3a** with 4 : 1 : 1 gave the highest yield of **4aaa** (entry 8). In other solvents, such as THF, toluene, MeCN, or pyridine, yields were even lower (entries 12–15).



Scheme 1 [2 + 2 + 1] Cycloaddition to form γ-butyrolactams.

We next investigated the scope of the reaction briefly (Table 2). The reaction of 4-octyne (**1b**) with **2a** and **3a** afforded correspondingly substituted γ-butyrolactam **4baa** in 66% isolated yield (entry 1). The cycloaddition is also compatible with aryl-substituted alkyne **1c** and provides cycloadduct **4caa** in 56% yield with a regioselectivity ratio of 2/1 (entry 2). The reaction with unsymmetrical alkynes such as **1d** and **1e** gave the products consisting of regioisomers in 1/1 and 2/1 ratio, respectively (entries 3 and 4), while bulky isopropyl substituted alkyne **1f** reacted with **2a** and **3a** to afford γ-butyrolactam **4faa** in 72% yield with a regioselectivity ratio of 7/1 (entry 5). Terminal alkynes, such as 1-octyne and phenylacetylene, failed to participate in the reaction, presumably due to rapid oligomerization of alkynes. The scope of the [2 + 2 + 1] cycloaddition was also explored by using various isocyanates. Either electron-donating or -withdrawing substituents on phenyl isocyanate tolerated the reaction conditions to afford correspondingly substituted cycloadducts in moderate yield (entries 6–10). However, alkyl isocyanates, such as cyclohexyl isocyanate and propyl isocyanate, reacted with **1a** and **2a** to provide γ-butyrolactam in poor yields (entries 11 and 12). It should be noted that isocyanates have no effects on the regioselectivity of the reaction. The reaction of **1a** and **3a** with ethyl acrylate (**2b**) or *tert*-butyl acrylate (**2c**) in place of methyl acrylate (**2a**) afforded γ-butyrolactam in lower yields but with better regioselectivity (entries 13 and 14). Therefore, the steric environment of the alkyne **1** and acrylate **2** dictated the regioselectivity of the reaction.

A plausible reaction pathway to account for the formation of γ-butyrolactam **4aaa** based on the observed results is outlined in Scheme 2. The catalytic cycle of the present reaction may consist of oxidative cyclization of nickel(0) with an alkyne **1** and an acrylate **2** to provide nickelacyclopentene complex **5a**, in which the steric repulsive interaction is minimal between the bulkier R^L and the IPr ligand on the nickel.[6,8] The preferential formation of complex **5a** may be attributed to a steric repulsive interaction between the bulky IPr ligand and alkyne **1**, which prevents formation of nickelacyclobutadiene complex *via* coordination of two molecules of alkyne **1** to a nickel metal center. Then, subsequent insertion of isocyanate **3** takes place, to give nickel(II) intermediate **6**. β-Hydride elimination would give **7**, in which a C–C double bond inserts into the hydride-nickel bond to provide **8**. Reductive elimination of **4** would regenerate the starting nickel(0).

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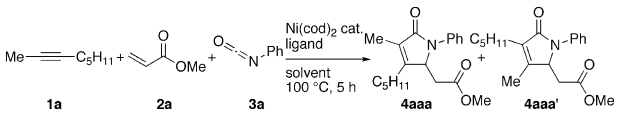
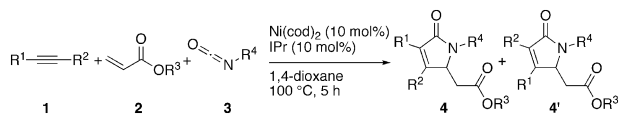
Table 1 Nickel-catalyzed [2 + 2 + 1] cycloaddition of **1a**, **2a** and **3a**[a]



Entry	Ligand	**1** (equiv.)	**2** (equiv.)	**3** (equiv.)	Solvent	Yield (%)
1	PPh_3	1	1	1	1,4-Dioxane	<1
2	PCy_3	1	1	1	1,4-Dioxane	<1
3	PMe_3	1	1	1	1,4-Dioxane	<1
4	IPr	1	1	1	1,4-Dioxane	56 (5/1)[b,c]
5	IMes	1	1	1	1,4-Dioxane	49 (1/1)[b,c]
6	SIPr	1	1	1	1,4-Dioxane	47 (4/1)[b,c]
7	IPr	2	1	1	1,4-Dioxane	68 (5/1)[b,c]
8	IPr	4	1	1	1,4-Dioxane	76 (5/1)[b,c]
9	IPr	6	1	1	1,4-Dioxane	67 (5/1)[b,c]
10	IPr	1	2	1	1,4-Dioxane	46 (5/1)[c,d]
11	IPr	1	1	2	1,4-Dioxane	50 (5/1)[b,c]
12	IPr	4	1	1	THF	72 (5/1)[b,c]
13	IPr	4	1	1	Toluene	56 (5/1)[b,c]
14	IPr	4	1	1	MeCN	<1 (5/1)[b,c]
15	IPr	4	1	1	Pyridine	<1 (5/1)[b,c]

[a] All reactions were carried out using $Ni(cod)_2$ (10 mol%), and ligand (10 mol%) in 2 mL of solvent (100 °C) unless otherwise noted. [b] Isolated yield based on acrylate **2a**. [c] Ratio of regioisomers (**4aaa**/**4aaa**′). [d] Yield based on alkyne **1a**.

Table 2 Nickel-catalyzed [2 + 2 + 1] cycloaddition[a]



Entry	R^1	R^2	R^3	R^4	**4**	Yield (%)[b]
1	Pr	Pr	Me	Ph	**4baa**	66
2	Me	Ph	Me	Ph	**4caa**	56 (2/1)[c]
3	CH_2OMe	Pr	Me	Ph	**4daa**	45 (1/1)[c]
4	CH_2CH_2OMe	Pr	Me	Ph	**4eaa**	69 (2/1)[c]
5	Me	*i*Pr	Me	Ph	**4faa**	72 (7/1)[c]
6	Me	C_5H_{11}	Me	4-MeO-C_6H_4-	**4aab**	56 (5/1)[c]
7	Me	C_5H_{11}	Me	4-CF_3-C_6H_4-	**4aac**	61 (5/1)[c]
8	Me	C_5H_{11}	Me	4-F-C_6H_4-	**4aad**	66 (5/1)[c]
9	Me	*i*Pr	Me	4-MeO-C_6H_4-	**4fab**	54 (7/1)[c]
10	Me	*i*Pr	Me	4-F-C_6H_4-	**4fac**	60 (7/1)[c]
11	Me	C_5H_{11}	Me	Pr	**4aae**	29 (5/1)[c]
12	Me	C_5H_{11}	Me	Cy	**4aaf**	24 (5/1)[c]
13	Me	C_5H_{11}	Et	Ph	**4aba**	63 (6/1)[c]
14	Me	C_5H_{11}	*t*Bu	Ph	**4aca**	28 (10/1)[c]

[a] All reactions were carried out using $Ni(cod)_2$ (10 mol%), ligand (10 mol%), **1** (2.0 mmol), **2** (0.5 mmol), and **3** (0.5 mmol) in 2 mL of 1,4-dioxane (100 °C). [b] Isolated yields. [c] Ratio of regioisomers (**4**/**4**′).

In conclusion, an unprecedented type of [2 + 2 + 1] cycloaddition reaction of alkynes, acrylates and isocyanates was successfully demonstrated using a nickel catalyst. The key intermediate is a nickelacycle **5** which would be formed *via* oxidative cyclization of Ni(0) with alkyne **1** and acrylate **2** in the presence of IPr ligands. Further studies of the detailed mechanism are currently underway in our laboratories.

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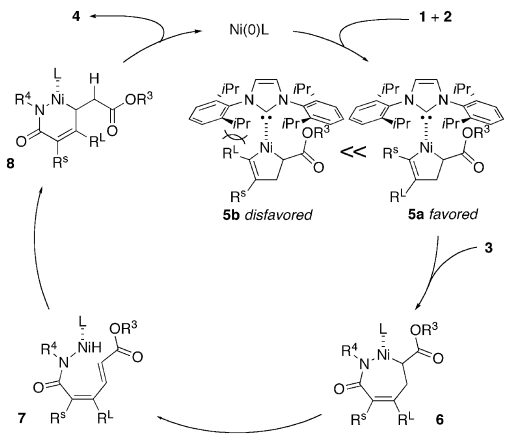

Scheme 2 Plausible reaction pathway.

Notes and references

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8 The alternative mechanism involving the initial coupling of alkyne and isocyanate with Ni(0)/IPr may not be ruled out.