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Nickel-iminophosphine-catalyzed [4 + 2] cycloaddition of enones with allenes: synthesis of highly substituted dihydropyrans†

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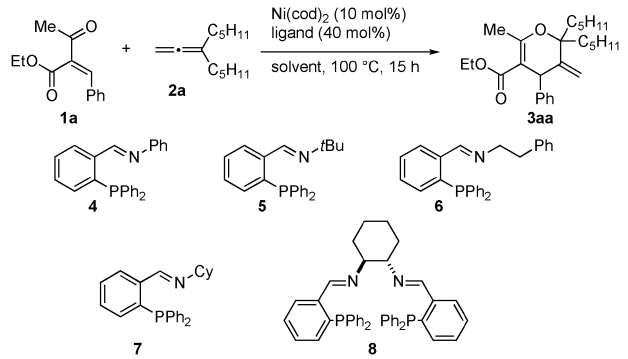
Enones were found to react with allenes intermolecularly in the presence of a catalytic amount of a nickel-iminophosphine complex to provide dihydropyrans *via* oxidative cyclization of an enone and Ni(0).

The hetero Diels–Alder reactions of α,β-unsaturated carbonyl compounds with carbon–carbon double bonds are a useful method for the synthesis of dihydropyrans, which are privileged structural subunits in numerous important natural products and in pharmaceuticals.[1,2] Although there are a large number of examples for syntheses of dihydropyrans by hetero Diels–Alder reactions, the use of an enol ether as an electron-rich heterodienophile is mandatory for sufficient transformation, and an example of utilization of other heterodienophiles has never been appeared in the literature.[3] Thus, the development of alternative methodologies, which would allow for straightforward access to structurally diverse dihydropyrans, remains an important research topic. Herein, we wish to report an unprecedented nickel-catalyzed [4 + 2] cycloaddition of enones with allenes to afford highly substituted dihydropyrans.

We recently reported that the Ni(0)/PMe_3 catalyst promotes [4 + 2] cycloaddition of enones with alkyne.[4] Thus, we first presumed that the same reaction conditions might be available for the cycloaddition of enones with allenes as well. Therefore, ethyl benzylidene acetoacetate (**1a**) was treated with 1,1-dipentylallene (**2a**), 10 mol% of $Ni(cod)_2$ and 40 mol% of PMe_3 in toluene at 100 °C for 15 h. However, this led to dihydropyran **3aa** only in 15% yield (Table 1, entry 1). The result prompted us to investigate efficient ligands for the transformation. Phosphine ligands, such as PPh_3, and PCy_3, did not afford cycloadduct **3aa**. However, to our delight, it was found through examination of various ligands that iminophosphines are highly efficient for the [4 + 2] cycloaddition.[5,6] Among the iminophosphines examined, cyclohexylamine-derived ligand **7** gave the best result (95% yield, entry 7). Trace or lower amounts of **3aa** were obtained in the cases of using **4**, **5**, and **8** in place of **7** (entries 4–8). Decreasing the amount of iminophosphine **7** to 20 mol% resulted in lowering the yield of cycloadduct **3aa** (entry 9). On screening the molecular ratio of **1a** and **2a** that was employed for cycloaddition, it was found that a ratio of **1a**/**2a** of 1 : 2.5 gave the highest yield of **3aa** (entries 7, 10, and 11). Finally, by changing the reaction solvent to 1,4-dioxane or MeCN, we obtained **3aa** in 99% yield (entries 12 and 13).

A range of substrates **1** was also tested in the reaction with allene **2a**; results are summarized in Table 2. Enones **1b** and **1c** also reacted with **2a** to furnish dihydropyrans **3ba** and **3ca** in 70% and 24% yields respectively (entries 2 and 3). However, cycloadduct **3ba** was obtained in 18% isolated yield due to decomposition during silica gel column chromatography.

Table 1 Nickel-catalyzed [4 + 2] cycloaddition of **1a** with **2a**[a]



Entry	Ligand	**2a** (equiv.)	Solvent	Yield[b] (%)
1	PMe_3	2.5	Toluene	15
2	PPh_3	2.5	Toluene	<1
3	PCy_3	2.5	Toluene	<1
4	**4**	2.5	Toluene	23
5	**5**	2.5	Toluene	<1
6	**6**	2.5	Toluene	72
7	**7**	2.5	Toluene	95
8	**8**	2.5	Toluene	<1
9	**7**[c]	2.5	Toluene	52
10	**7**	1.5	Toluene	80
11	**7**	3.0	Toluene	89
12	**7**	2.5	1,4-Dioxane	99
13	**7**	2.5	MeCN	99
14	**7**	2.5	Pyridine	58

[a] All reactions were carried out using **1a** (0.2 mmol), **2a**, $Ni(cod)_2$ (10 mol%), and ligand (40 mol%) in 2 mL of solvent (100 °C) unless otherwise noted. [b] NMR yield base on enone **1a**. [c] 20 mol% of **7**.

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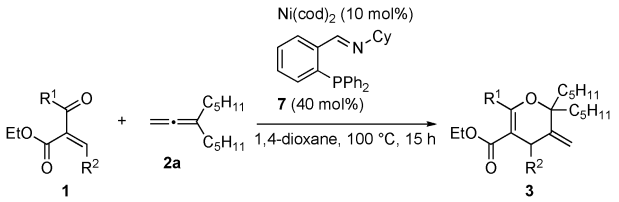
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1cc10890e

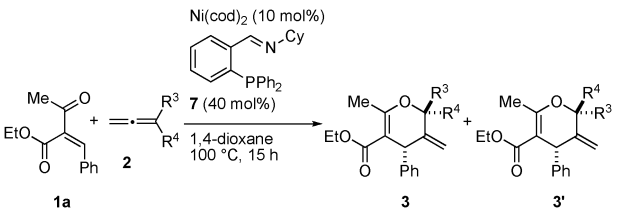
Table 2 The scope of the [4 + 2] cycloaddition[a]



Entry	R^1	R^2	1	3	Yield[b] (%)
1	Me	Ph	**1a**	**3aa**	99 (98)
2	Ph	Ph	**1b**	**3ba**	70 (18)
3	*t*Bu	Ph	**1c**	**3ca**	24 (23)
4	Me	4-MeO-C_6H_4	**1d**	**3da**	99 (73)
5	Me	4-CF_3-C_6H_4	**1e**	**3ea**	61 (60)
6	Me	Pr	**1f**	**3af**	<1

[a] All reactions were carried out using **1a** (0.2 mmol), **2a** (0.5 mmol), $Ni(cod)_2$ (10 mol%), and **7** (40 mol%) in 2 mL of 1,4-dioxane (100 °C) for 15 h unless otherwise noted. [b] NMR yield base on enone **1a**. Isolated yields are given in parentheses.

Table 3 The [4 + 2] cycloaddition of **1a** with various allenes **2**[a]

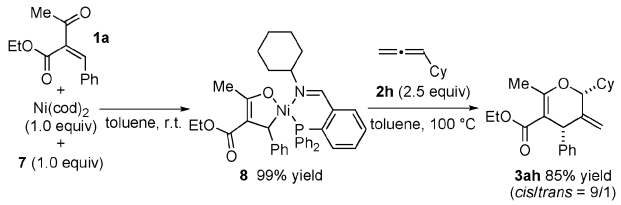


Entry	R^3	R^4	2	3	Yield[b] (%)
1	C_5H_{11}	C_5H_{11}	**2a**	**3aa**	99 (98)
2	Me	Me	**2b**	**3ab**	36 (40)
3	H	C_5H_{11}	**2c**	**3ac**/**3ac′**	84 (91) (1/1)[c]
4	H	CH_2CH_2Ph	**2d**	**3ad**/**3ad′**	88 (80) (1/1)[c]
5	H	CH_2CH_2CN	**2e**	**3ae**/**3ae′**	99 (95) (2/3)[c]
6	H	CH_2CH_2OAc	**2f**	**3af**/**3af′**	87 (76) (2/3)[c]
7	H	$CH_2CH_2OSitBuPh_2$	**2g**	**3ag**/**3ag′**	93 (94) (1/2)[c]
8	H	Cy	**2h**	**3ah**/**3ah′**	99 (94) (9/1)[c]

[a] All reactions were carried out using **1a** (0.2 mmol), **2a** (0.5 mmol), $Ni(cod)_2$ (10 mol%), and **7** (40 mol%) in 2 mL of 1,4-dioxane (100 °C) for 15 h unless otherwise noted. [b] NMR yield base on enone **1a**. Isolated yields are given in parentheses. [c] Ratio of *cis* **3**/*trans* **3′**.

β-Aryl substituted enones possessing an electron-donating or -withdrawing group on the phenyl ring also provided corresponding cycloadducts in good to moderate yields (entries 4 and 5), whereas β-alkyl substituted enones fail to participate in the reaction.[7]

We next investigated the scope of the reaction using various allenes; results are summarized in Table 3. Under the same reaction conditions, highly volatile 1,1-dimethylallene **2b** also reacted with **1a** to furnish cycloadduct **3ab** in 36% yield (entry 2). The reaction of **1a** with mono-substituted allenes, such as **2c** and **2d**, gave the dihydropyrans consisting of regioisomers in 1/1 ratio (entries 3 and 4). Allenes possessing functional groups, such as nitrile, acetoxy, and siloxy, also tolerated the reaction conditions and afforded the correspondingly substituted dihydropyrans in high yield (entries 5–7). Although distinct directing effects of such functional groups in regioselectivity



Scheme 1 Formation of oxa-nickelacycle *via* oxidative cyclization.

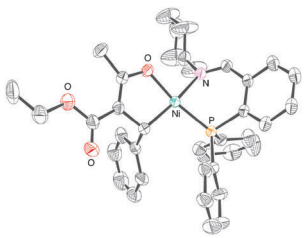
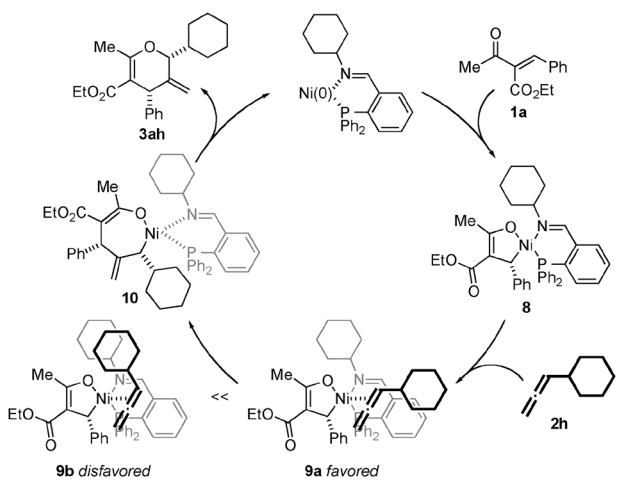


Fig. 1 ORTEP drawing of **8**.

on the reaction were not observed, it was found that the cycloaddition reaction of **1a** with bulky cyclohexyl-substituted allene **2h** gave the dihydropyrans **3ah** in 99% yield with high regioselectivity (entry 8). The *cis*-configuration of **3ah** was confirmed by X-ray crystal structure analysis.[8]

We then conducted stoichiometric reactions of **1a** with $Ni(cod)_2$ and iminophosphine **7** to obtain insight into the reaction mechanism. The reaction of ethyl benzylidene acetoacetate (**1a**) with $Ni(cod)_2$ and iminophosphine **7** at 25 °C gave an oxa-nickelacycle **8** quantitatively (Scheme 1).[9] The molecular structure of **8** was confirmed by the X-ray crystal structure analysis, which showed that the nickel(II) complex has a square planar molecular geometry (Fig. 1). The coordination geometry of **8** with the oxygen atom *trans* to the phosphorous atom is rationalized by *trans* influence, considering that the phosphines are one of the strongest donor ligands.[10] Treatment of oxanickelacycle **8** with allene **2h** in toluene (100 °C, 15 h) afforded the dihydropyran **3ah** in 85% isolated yield consisting of regioisomers in 9/1 ratio. Thus, the catalytic reaction to form dihydropyran **3ah** can be rationalized as arising



Scheme 2 Plausible reaction mechanism for cycloaddition of **1a** with **2h**.

from oxidative cyclization of nickel(0) to an enone **1a** to form oxa-nickelacycle **8** (Scheme 2).[11] Subsequent coordination of allene **2h** takes place to give intermediate **9a**; here, the steric repulsive interaction is minimal between two cyclohexyl groups of both **2h** and **8**. Insertion of an allene into the C–Ni bond leads to the seven-membered oxa-nickelacycle **10**, which undergoes reductive elimination to give **3ah** and a Ni(0) complex.

In summary, we have developed a new nickel-catalyzed [4 + 2] cycloaddition reaction of enones with allenes to provide highly substituted dihydropyrans. Iminophosphine was found to be a highly active ligand for the reaction; enones are susceptible to oxidative cyclization of nickel(0) in the presence of an iminophosphine ligand, and such reactions allow intermolecular cycloaddition with allenes. Further investigations on the potential of the developed cycloaddition and detailed mechanistic studies of the catalytic reaction mechanism are currently underway in our laboratory.[12]

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6 The use of other bidentate ligands, such as dppf, dppp, binap, bpy, did not afford any product.

7 Neither benzylidene-substituted pentane-2,4-dione nor diethyl malonate participated in the cycloaddition with allene **2a** even for prolonged reaction times, and both were recovered unchanged quantitatively. A stoichiometric reaction of such enones with $Ni(cod)_2$ and iminophosphine **7** did not afford oxa-nickelacycle and resulted in no reaction. Thus, α-ester-substituted α,β-unsaturated ketone will be a suitable substrate for oxa-nickelacycle formation and cycloaddition with allenes.

8 For details see ESI†.

9 For crystallographic evidence for the formation of oxa-nickelacycles, see: (*a*) H. H. Karsch, A. W. Leithe, M. Reisky and E. Witt, *Organometallics*, 1999, **18**, 90; (*b*) K. K. D. Amarasinghe, S. K. Chowdhury, M. J. Heeg and J. Montgomery, *Organometallics*, 2001, **20**, 370; (*c*) J. Montgomery, K. K. D. Amarasinghe, S. K. Chowdhury, E. Oblinger, J. Seo and A. V. Savchenko, *Pure Appl. Chem.*, 2002, **74**, 129; (*d*) S. Ogoshi, M. Oka and H. Kurosawa, *J. Am. Chem. Soc.*, 2004, **126**, 11802; (*e*) H. P. Hratchian, S. K. Chowdhury, V. M. Gutierrez-Garcia, K. K. D. Amarasinghe, M. J. Heeg, H. B. Schlegel and J. Montgomery, *Organometallics*, 2004, **23**, 4636; (*f*) S. Ogoshi, M. Ueta, T. Arai and H. Kurosawa, *J. Am. Chem. Soc.*, 2005, **127**, 12810; (*g*) S. Ogoshi, M. Nagata and H. Kurosawa, *J. Am. Chem. Soc.*, 2006, **128**, 5350; (*h*) S. Ogoshi, K. Tonomori, M. Oka and H. Kurosawa, *J. Am. Chem. Soc.*, 2006, **128**, 7077; (*i*) S. Ogoshi, T. Arai, M. Ohashi and H. Kurosawa, *Chem. Commun.*, 2008, 1347.

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12 As a result of preliminary experiments, we found that cycloaddition of **1a** with **2a** in the presence of $Ni(cod)_2$/(*S*,*S*)-iPr-foxap afforded **3aa** with 54% ee in 18% yield. Further modifications of chiral iminophosphine ligands to improve enantioselectivity and yield are underway.

