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ORIGINAL ARTICLE

Synthesis of polysubstituted β-amino cyclohexane carboxylic acids via Diels–Alder reaction using Ni(II)-complex stabilized β-alanine derived dienes

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Abstract This paper describes the design and synthesis of a new class of β-alanine derived dienes stabilized by Ni(II)-complex. Preliminary study of their Diels–Alder cycloaddition reactions with several types of dienophiles demonstrates their significant synthetic potential for the preparation of various polyfunctional β-aminocyclohexane carboxylic acids.

Keywords Diels–Alder reaction · Nickel (II) · β-Alanine · β-Aminocyclohexane carboxylic acids

Introduction

The Diels–Alder reaction is one of the most magnificent discoveries in organic chemistry by bridging the realms between acyclic and cyclic compounds (Diels and Alder 1928). Although numerous variants on this reaction have been studied, the potential synthetic wealth of this approach for preparation of six-membered cyclic compounds has still not been completely explored (Takao et al. 2005). In particular, application of Diels–Alder reactions for the preparation of β-amino cyclohexane carboxylic acids is one of the least studied areas (Juaristi and Soloshonok 2005). Current established methods usually rely on indirect introduction of the desired amino group via nitro (Pitacco et al. 1977) or carboxylic (Furuta et al. 1987) functionalities on the starting dienophile. Besides increasing synthetic steps, these approaches required operationally inconvenient high-pressure reduction or Curtius protocols (Pitacco et al. 1977; Furuta et al. 1987). One may agree that methods using dienes/dienophiles directly containing protected amino group would be methodologically more straightforward and therefore practically attractive. However, this approach presents several synthetic challenges associated, most notably, with low stabilities of the required amino-containing starting compounds (Juaristi and Soloshonok 2005). To the best of our knowledge, there are only two reports in the literature representing this direct approach. As shown in Scheme 1, β-amino acid **3** can be prepared by a Lewis acid-catalyzed cycloaddition between amino-containing diene **2** and acrylic acid derivative **1** (Wipf and Wang 2000). Alternatively, dienophile **4**, derived from glycine, can react at room temperature with activated dienes (Danishefsky's diene or cyclopentadiene) **5** to afford a particular type of α-/β-amino acids **6** in a 5-step procedure (Bunuel et al. 1996a, b). Remarkably, this type of Diels–Alder reactions still remain underdeveloped and presents an intellectually challenging line of research. Furthermore, besides methodological novelty, this area of research has additional aspects of general synthetic

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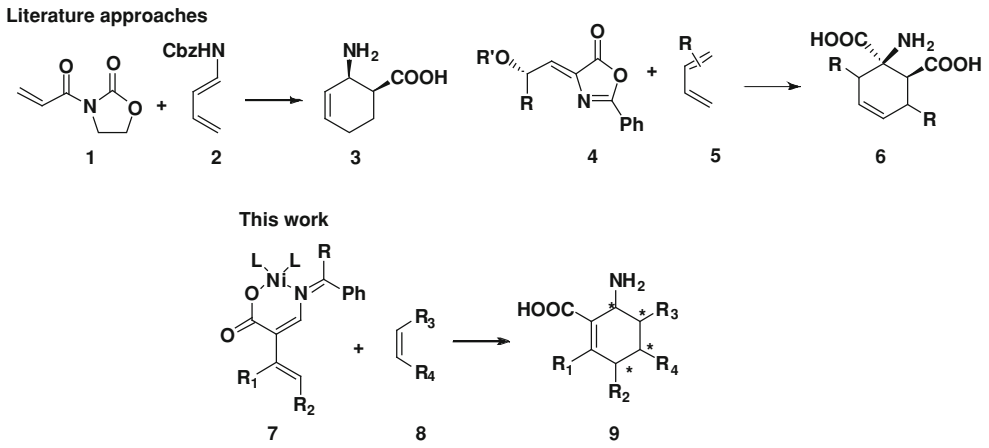


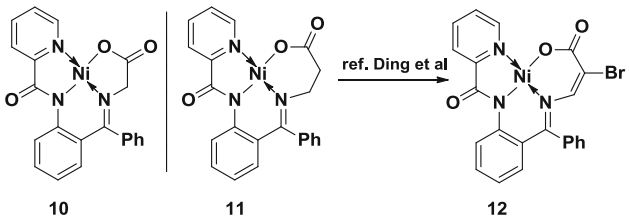
Scheme 1 Methodologically different approaches for preparation of *β*-amino cyclohexane carboxylic acids via Diels–Alder reaction

importance (Chola and Masesane 2008; Csende et al. 2008; Songis et al. 2008), considering a notable role of *β*-amino cyclohexane carboxylic acid motif in the chemistry of natural products (Oki et al. 1989; Iwamoto et al. 1990) and *β*-peptides (Epand et al. 2004; Hayen et al. 2004).

Ni(II)-complexes of glycine of type **10** (Scheme 2) (Deng et al. 2007; Ueki et al. 2003a, b; Soloshonok et al. 2005a, b; Ellis et al. 2005, 2006) proved to be of quite general application for preparation of various tailor-made (Soloshonok et al. 1999a, b) α-amino acids (Soloshonok 2002; Soloshonok et al. 2000a; Yamada et al. 2006). Homologation of glycine moiety in **10** can be conducted with high chemical yields and stereoselectivity via alkylation (Soloshonok et al. 1992, 2001a; Ellis et al. 2003a; Wang et al. 2011), Michael (Soloshonok et al. 1999c, 2000b, 2005a), Mannich (Soloshonok et al. 1997; Wang et al. 2008) and aldol (Soloshonok et al. 1995, 1996a, b) addition reactions. Of particular importance is that the homologation of **10** can be performed under operationally convenient conditions (Ellis et al. 2003b; Soloshonok et al. 2004, 2006), allowing synthesis of target α-amino acids on large scales (Qiu et al. 2000; Soloshonok et al. 2001b; Tang et al. 2000).

Results and discussion

On the other hand, the chemistry and synthetic potential of the corresponding complex **11**, derived from *β*-alanine, still remains virtually unexplored. Our initial results in this area convincingly demonstrate that compounds of this type hold significant promise for practical preparations of various *β*-amino acids (Ding et al. 2009). In particular, we have recently developed a convenient procedure for the preparation of the corresponding α-bromo-α,*β*-unsaturated analog **12,** and demonstrated its application for preparation of

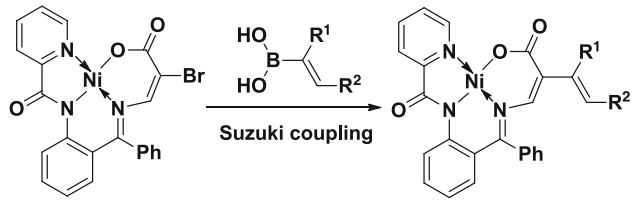


Scheme 2 Ni(II)-complexes of glycine (**10**), *β*-alanine (**11**) and its α,*β*-unsaturated α-bromo derivative **12**

α-aryl-substituted *β*-amino acids via two-step alkylation-reduction sequence (Ding et al. 2009). Continuing our work on synthetic applications of *β*-alanine derived complexes **11** and **12**, we found that the bromine atom in **12** can be easily substituted with boronic acids containing unsaturated moieties by Suzuki coupling reaction giving rise to new compounds of type **13** containing 1,3-diene system (Table 1). Using the reported conditions, the reaction proceeded satisfactorily when reacting **12** with various boronic acids in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 in toluene and water under microwave irradiation (Ding et al. 2009). As shown in Table 1, a variety of acyclic and cyclic boronic acids can participate in the reaction to afford the corresponding products **13** and **16a–g** in moderate to excellent yields (73–93 %, entries 1–8). While a relatively lower yield (76 %, entry 8) was obtained in the case of *tert*-butyl related boronic acid presumbably due to a steric effect.

Ni(II)-complex **13** (R^1 = Me, R^2 = H) (Table 2), containing a structurally simple diene residue, and dienophile *N*-ethylmaleimide **14** were used as the model substrate to study the possibility to conduct the corresponding Diels–Alder cycloaddition reactions. We found that the formation of target product **15** takes place upon heating of the starting compounds in toluene with a yield of 60 % (Table 2, entry 1). Higher temperatures and longer reaction time favored the formation of cycloaddition product **15** allowing its

Table 1 Synthesis of complexes **13** and **16a–g** containing β-alanine and 1,3-diene fragments

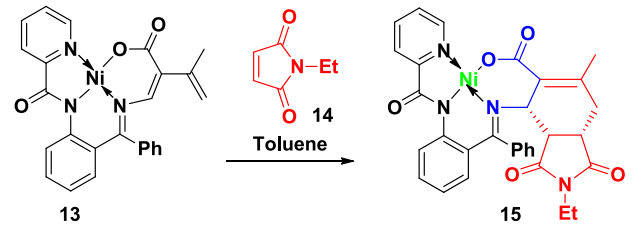


12 13 and 16a-g

Entry	R^1	R^2	Dienes	Yield (%)
1	CH_3	H	**13**	82
2	H	H	**16a**	73
3	H	CH_3	**16b**	84
4	H	Propyl	**16c**	91
5	H	Hexyl	**16d**	93
6	H	Cyclopropyl	**16e**	90
7	H	Cyclohexyl	**16f**	87
8	H	$C(CH_3)_3$	**16g**	76

Reactions were run with 1.31 mmol of **12**, 3.9 mmol of boric acids, 3.9 mmol Na_2CO_3 in 5 mL of toluene and 2 mL of water with 0.014 mmol of $Pd(PPh_3)_4$ at 70 °C under microwave irradiation

Table 2 Diels–Alder reaction of the nickel(II) complex **13** with *N*-ethylmaleimide



13 15

Entry	Temperature (°C)	Time (h)	Yield (%)
1	80	12	60
2	120	18	85
3	120	24	92
4	120	24	45[a]

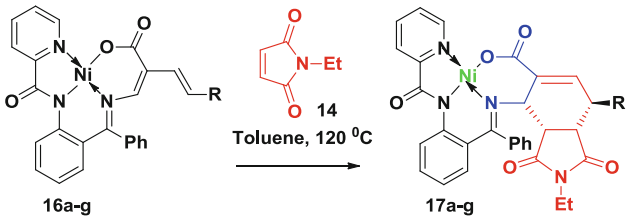
Reactions were conducted using 0.1 mmol of diene **13** and 0.3 mmol of dienophiles in 2 mL of toluene

[a] 1.0 equiv of BF_3 was added as the Lewis acid

preparation in 92 % yield (Table 2, entry 3). Attempt to further improve the reaction outcome by catalysis with Lewis acid BF_3 was less successful and only 45 % yield of the product **15** was obtained. This is mainly because the Ni(II)-complex is unstable under acidic conditions resulting in the decomposition and the recovery of the starting material PBP (Table 2, entry 4).

With these promising results in hand, we examined further the generality of Diels–Alder reactions using a series of Ni(II)-complexes **16a–g** containing structurally

Table 3 Diels–Alder reactions of the dienophile *N*-ethylmaleimide with different dienes



16a-g 17a-g

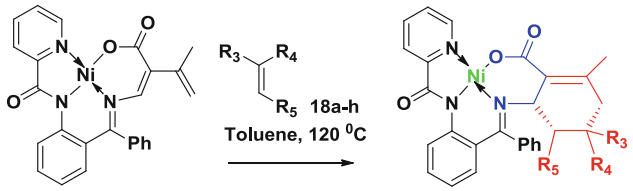
Entry	Dienes	R	Products	Yield (%)
1	**16a**	H	**17a**	93
2	**16b**	CH_3	**17b**	90
3	**16c**	Propyl	**17c**	88
4	**16d**	Hexyl	**17d**	85
5	**16e**	Cyclopropyl	**17e**	90
6	**16f**	Cyclohexyl	**17f**	82
7	**16g**	$C(CH_3)_3$	**17g**	76

Reactions were conducted using 0.1 mmol of dienes **16a–g** and 0.3 mmol of dienophile **14** in 2 mL of toluene at 120 °C for 24 h

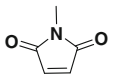
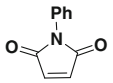
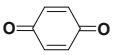
diverse groups. The results summarized in Table 3 demonstrated that the reaction under study has rather general application. Substrates **16a–g** bearing various alkyl and cycloalkyl groups gave the target products **17a–g** in excellent yields (76–93 %, entries 1–7). Acyclic and cyclic substituents on the starting dienes **16b–g** showed no dramatic influence on the yields. Remarkably, this cycloaddition reaction was also tolerated in the presence of sterically bulky *tert*-butyl group, though the reaction rate was noticeably slower and resulted in lower isolated yield of the corresponding product **17g** (76 %, entry 7).

Another aspect of the synthetic generality of this Diels–Alder reaction was explored by investigating the cycloadditions between dienes of type **13** and various dienophiles **18**. The results were shown in Table 4. First, we examined the effects of the *N*-substituent of maleimide on the Diels–Alder reaction using derivatives **18a** and **18b** bearing methyl and phenyl groups, respectively. Expectedly, the reaction of *N*-methylmaleimide **18a** with Ni(II)-complex **13** gave the cycloaddition product **19a** with 92 % yield (entry 1). While a relatively lower yield was obtained when the dienophile was phenyl-substituted maleimide presumably because of the steric effect (72 %, entry 2). These results suggested that the cyclic dienophiles of type **14** showed good reactivities and provide reliable access to the corresponding β-amino acids derivatives. However, only trace amount of the product **19c** (entry 3) was obtained when benzoquinone was used as the dienophile. We then decided to concentrate our further study on acyclic derivative **18d–h** containing electronically activating as well as deactivating functional groups. Cycloadditions of diene **13** with dienophiles **18d** and **18e**, bearing electron-

Table 4 Diels–Alder reactions of the diene **13** with various dienophiles



13 19a-h

Entry	Dienophiles	R^3	R^4	R^5	Products	Yield (%)
1	**18a**				**19a**	92
2	**18b**				**19b**	72
3	**18c**				**19c**	Trace[a]
4	**18d**	H	$COOCH_3$	$COOCH_3$	**19d**	58
5	**18e**	H	CN	CN	**19e**	61[b]
6	**18f**	COOEt	H	H	**19f**	Trace[a]
7	**18g**	CH_3	CH_3	CH_3	**19g**	0
8	**18h**	OEt	H	H	**19h**	0

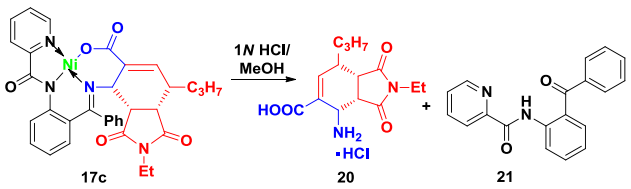
Reactions were run with 0.1 mmol of dienes **13** and 0.3 mmol of dienophiles **18** in 2 mL toluene at 120 °C for 24 h

[a] Detected by LC/MS

[b] Not isolated yield. Detected by LC/MS. The product was not stable during the workup

withdrawing substituents on both sides of the double bond, occurred with relatively low yields of 58 % (entry 4) and 61 % (entry 5), respectively. These results clearly suggested that this approach can be optimized for the efficient preparation of *β*-amino acid derivatives of type **19c–e**. In sharp contrast, the reaction of dienophile **18f**, bearing only one activating substituent (entry 6) proceeded very slowly and only trace amount of the product was detected by LC/MS. No product was observed when the dienophiles were alkyl- or electron-donating substituted (Table 4, entries 7 and 8). These results clearly pointed to obvious limitation of this approach in terms of generality of the dienophile type.

Taking into account that the cycloaddition products **15**, **17** and **19** are structurally new type of Ni(II) complexes, we needed to demonstrate that they can be reliably disassembled to release the target *β*-amino acid. To this end, we treated product **17c** under the standard disassembly conditions by heating suspension of **17c** in 1 N HCl/MeOH. Decomposition of complex **17c** took place quite in a usual manner allowing isolation of the target *β*-amino acid **20** in 90 % yield along with quantitative recovery of ligand **21**, which can be recycled to prepare starting *β*-alanine derived Ni(II) complex **11** (Scheme 3).



17c 20 21

Scheme 3 Disassembling of nickel(II) complex **17c** to release target *β*-amino acid **20** and recovery of the ligand **21**

Conclusion

In conclusion, we have successfully developed a new type of Ni(II) complex stabilized *β*-alanine derived dienes and outlined their reactivity with different types of dienophiles. The results presented in this work convincingly suggested that the designed dienes have a significant synthetic potential for highly diastereospecific preparation of polyfunctional *β*-amino-cyclohexanecarboxylic acids via Diels–Alder reaction. Further work on asymmetric version of this approach is currently under study and will be reported in a due course.

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