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Selective Michael–Aldol Reaction by Use of Sterically Hindered Aluminum Aryloxides as Lewis Acids: An Easy Approach to Cyclobutane Amino Acids

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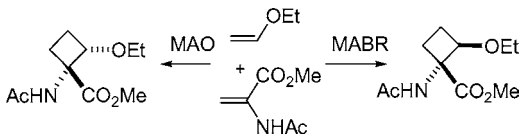
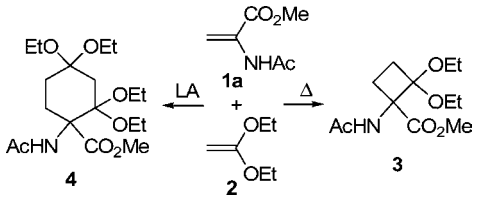
ABSTRACT



A formal [2 + 2] cycloaddition of 2-amidoacrylates with monosubstituted donor olefins, including its asymmetric version, is described. The stereoselectivity of this reaction can be modulated by the use of sterically hindered aluminum aryloxides or methylaluminoxane as Lewis acids. The reaction was applied to the synthesis of both stereoisomers of 2-benzyloxycyclobutane-α-amino acid, which are protected serine analogues c_4Ser(OBn).

The use of small-ring systems, especially cyclobutane derivatives, as molecular building blocks has gained increasing significance in the past decade.[1] Although cyclobutane derivatives are easily accessible by several preparative methods, the amino acids of the cyclobutane series have received relatively little attention.[2] From 1980,[3] and particularly after some derivatives were found to be potent neurotransmitters, synthetic efforts were extended to a whole range of cyclobutane amino acids. Nevertheless, methods for the synthesis of 2-substituted cyclobutane amino acids have not received the same level of interest. In this context, we have recently reported the synthesis of some cyclobutane amino acid derivatives that are conformationally restricted analogues of serine (c_4Ser) by a formal [2 + 2] cycloaddition from methyl 2-acetamidoacrylate (**1a**) and 1,1-diethoxyethylene (**2**). When the same reaction was performed in the presence of Lewis acids (LAs), the double addition was achieved giving cyclohexane **4** (Scheme 1).[4] To explore the reactivity of olefin **1a**, we performed the thermal reaction with vinyl ethers but did not achieve positive results. The use of LAs in reactions between acrylates and vinyl ethers to furnish cyclobutane rings by a Michael−aldol sequence

Scheme 1. Reaction of Olefins **1a** and **2**



(1) (a) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485. (b) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449.

(2) (a) Avontins, F. *Russ. Chem. Rev.* **1993**, *62*, 897. (b) Gaoni, Y. *Org. Prep. Proc. Int.* **1995**, *27*, 185.

(3) Bell, H. A.; Qureshi, M. Y.; Pryce, R. J.; Janzen, D. H.; Lemke, P.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 1409.

(4) Avenoza, A.; Busto, J. H.; Canal, N.; Peregrina, J. M. *Chem. Commun.* **2003**, 1376.

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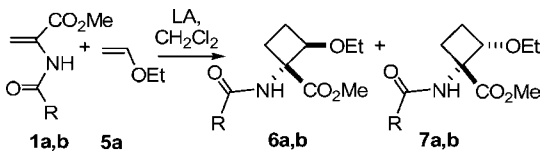
has recently been investigated. Indeed, Takasu, Ihara, and co-workers reported the catalytic cycloaddition reaction of silyl enol ethers.[5]

We envisioned the Michael−aldol reaction between olefin **1a** and ethyl vinyl ether (**5a**) in conjunction with several LAs. A broad screening of a number of LAs, including $AlCl_3$, $EtAlCl_2$, Et_2AlCl, $AlMe_3$, and $ZnCl_2$, was undertaken. Cyclobutane products were not formed in any of these cases and only starting material or polymerization products were obtained. In recent years, the use of bulky aluminum Lewis acids has grown because the steric effect associated with these reagents plays an important role in selective organic synthesis.[6] In our case, the best result in the cycloaddition of **1a** with **5a** was obtained using methylaluminum bis(4-bromo-2,6-di-*tert*-butyl phenoxide) (MABR) as the LA in CH_2Cl_2 at room temperature to give 93% yield of a mixture of cycloadducts **6a** and **7a** (Table 1, entry 1). The high selectivity gave compound **6a**, in which the ethoxy and ester groups are in a cis disposition, as the major stereoisomer (96/4).

Table 1. Effect of the Sterically Hindered Aluminum Lewis Acids in the Michael−Aldol Reaction



entry	LA[a]	olefin	R	T (°C)	time (h)	yield (%)	ratio of **6a**,**b**/**7a**,**b**
1	MABR	**1a**	Me	rt	7	93[b]	96/4[b]
2	MABR	**1a**	Me	rt	0.25	45[c]	88/12[c]
3	MABR	**1a**	Me	rt	0.08	15[c]	68/32[c]
4	MABR	**1a**	Me	rt	2	86[c]	96/4[c]
5	MABR	**1a**	Me	rt	7	56[b]	65/35[b]
6	MABR	**1a**	Me	−20	7	19[c]	70/30[c]
7	MABR	**1a**	Me	0	7	77[c]	78/22[c]
8	MABR	**1a**	Me	40	7	44[c]	98/2[c]
9	MAPH	**1a**	Me	rt	4	34[c]	25/75[c]
10	MAP	**1a**	Me	rt	6	3.5[d]	60/40[d]
11	MAM	**1a**	Me	rt	16	41[d]	28/72[d]
12	MAM	**1a**	Me	0	16	17[d]	9/91[d]
13	MAO	**1a**	Me	rt	16	53[b]	7/93[b]
14	MABR	**1b**	CF_3	−20	16	66[d]	>98/2[d]
15	MAO	**1b**	CF_3	−20	16	51[b]	7/93[b]

[a] All reactions were made with 2.0 equiv of LA, except entry 5 (1.1 equiv) and entries 13 and 15 (4 mL of MAO for 0.7 mmol of **1a**,**b**). [b] Yield and ratio after chromatography. [c] Conversion (%) and ratio measured by HPLC on the crude mixture. [d] Conversion (%) and ratio measured by integration of the H-2 proton signal in the ^1H NMR spectra of the crude mixture.

The structure of **7a** was confirmed by X-ray diffraction,[7] and the stereochemistry of **6a** was verified by NOE experiments. The use of short reaction times makes the ratio more favorable in terms of compound **7a** (Table 1, entries 2 and 3). It was observed that reactions carried out at low temperature resulted in a decrease in both the yield and selectivity (Table 1, entries 6 and 7). Higher temperatures gave the same selectivities but lower yields, mainly due to polymerization reactions (Table 1, entry 8). Alternatively, when the reaction was carried out with less than 2 equiv of LA, the yield and the selectivity decreased (Table 1, entry 5), and with less than 1 equiv, the reaction did not progress. These data could indicate that the compound **7a** is probably the kinetically favored product.

On the other hand, although methylaluminoxane (MAO) was found to be an efficient cocatalyst for olefin polymerization reactions,[8] few applications as a catalyst for nonpolymerization processes in organic synthesis have been reported.[9] Taking into account that Yamamoto used MAO as a very strong and quite bulky Lewis acid in Diels−Alder cycloadditions,[9a] we decided to explore its behavior in the [2 + 2] reaction. Surprisingly, the use of MAO (Table 1, entry 13) led to inversion of selectivity.

The effect of an amide group in the acceptor olefin was also investigated (Table 1, entries 14 and 15), therefore applying the best conditions used with olefin **1a**, we tested the reaction of methyl 2-trifluoroacetamidoacrylate (**1b**) with donor olefin **5a**, proving that this electron-withdrawing amide favors the reactivity since it is possible to carry out the reaction at low temperature (Table 1, entries 6 and 14). The high selectivity observed was again in the same direction as those obtained with olefin **1a**, giving exclusively the adduct **6b** with MABR and **7b** with MAO.

The influence of sterically hindered phenols was studied by using several LAs such as methylaluminum bis(2,6-diphenylphenoxide) (MAPH), methylaluminum bisphenoxide (MAP), and methylaluminum bis(2,4,6-trimethylphenoxide) (MAM). The yield was found to decrease when the spatial requirement was lower, and with MAPH and MAM, selectivity inversion was observed; therefore, compound **7a** became the major product (Table 1, entries 9, 11, and 12). However, the widely used Yamamoto catalyst aluminum tris(2,6-diphenylphenoxide) (ATPH)[10] did not produce any reaction. Moreover, the reaction did not take place when the NHAc group of **1a** was replaced by NHBoc. These facts, together with the evolution of gas in the reaction (probably methane) and the literature precedents,[11] lead us to propose the formation of an amidate metallacyclobutane involving an elimination−condensation reaction sequence[11a] (Scheme 2).

(5) (a) Takasu, K.; Ueno, M.; Inanaga, K.; Ihara, M. *J. Org. Chem.* **2004**, *69*, 517. (b) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2004**, *126*, 1352. (c) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2005**, *127*, 3668.

(6) (a) Ito, H.; Nagahara, T.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 994. (b) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924.

(7) See CIF files for **7a**, **8e**, **8h**, **12ai**, and **13ca** in Supporting Information.

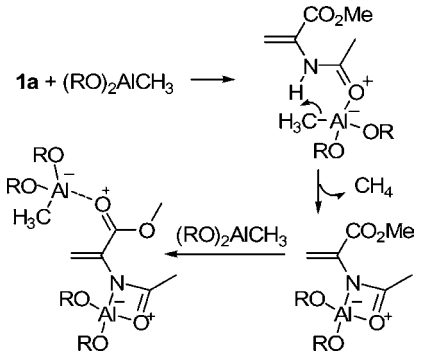
(8) Zurek, E.; Ziegler, T. *Prog. Polym. Sci.* **2004**, *29*, 107.

(9) (a) Akakura, M.; Yamamoto, H. *Synlett* **1997**, 277. (b) Negishi, E.; Tan, Z.; Liang, B.; Novak, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5782.

(10) Saito, S.; Nagahara, T.; Shiozawa, M.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6200.

(11) (a) Power, M. B.; Bott, S. G.; Clark, D. L.; Atwood, J. L.; Barron, A. R. *Organometallics* **1990**, *9*, 3086. (b) Huang, B. H.; Yu, T. L.; Huang, Y. L.; Ko, B. T.; Lin, C. C. *Inorg. Chem.* **2002**, *41*, 2987.

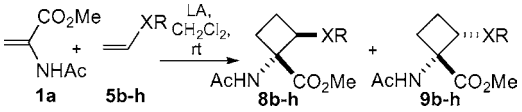
Scheme 2. Reaction of Olefin **1a** with LA



After an analysis of the MABR−**1a** complex (1:1) by ^{13}C NMR spectroscopy, we observed the loss of the methyl signal from the LA (−8.0 ppm) and a downfield displacement of 3.4 ppm in the carbonyl carbon signal of the amide. These changes provide further evidence of the formation of the metallacyclobutane.[11a] On the other hand, a similar study on the MABR−**1a** complex (2:1) showed that the methyl signal from the LA (−8.0 ppm) appeared and that the two carbonyl carbon (amide an ester) signals are shifted downfield (8.4 and 13.0 ppm, respectively). These facts can be interpreted in terms of coordination of the second equivalent of MABR to the carbonyl oxygen of the ester, which probably causes a decrease in the LUMO energy of this olefin[12] and therefore makes the reaction more effective. In summary, the presence of 2 equiv of a bis-aryloxide compound of aluminum is required to obtain a good yield of cyclobutane adducts.

With the aim of extending the scope of this reactivity, we performed the reaction of **1a** with other monosubstituted donor olefins **5b**−**h**. The results of these experiments are shown in Table 2. As it was observed with donor olefin **5a**, similar results were obtained in the reaction of olefin **1a** with vinyl thioether **5h**, including the stereoselectivity inversion promoted by MAO (Table 2, entries 9 and 10). The yields of the cyclobutane fluctuated in the range 39−72%, and the high selectivities were always in favor of stereoisomers **8b**−**h**, when MABR was used, as confirmed by NOE experiments, and selectivity inversion was observed when MAO or MAPH were used (Table 2, entries 2, 7, and 10). In addition, **8e** and **8h** structures were determined by X-ray diffraction.[7]

Table 2. Effect of the Vinyl Ether in the Michael−Aldol Reaction

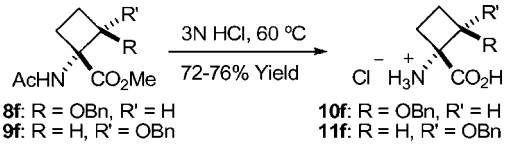


entry	LA	XR (vinyl ether)	time (h)	yield (%) [a]	ratio of **8**/**9**[a]
1	MABR	*O*-propyl (**5b**)	6	65	>98/2
2	MAO	*O*-propyl (**5b**)	24	72	>2/98
3	MABR	*O*-butyl (**5c**)	8	68	95/5
4	MABR	*O*-isobutyl (**5d**)	20	69	>98/2
5	MABR	*O*-cyclohexyl (**5e**)	6	56	>98/2
6	MABR	*O*-benzyl (**5f**)	15	62	90/10
7	MAPH	*O*-benzyl (**5f**)	7	39	32/68
8	MABR	*O*-trimethylsilyl (**5g**)	20	59	91/9
9	MABR	*S*-ethyl (**5h**)	8	56	65/35
10	MAO	*S*-ethyl (**5h**)	20	61	7/93

[a] Yield and ratio measured by ^1H NMR spectroscopy of the H-2 proton in the cyclobutane ring after column chromatography.

As an example of the application of this reaction in the preparation of biologically interesting compounds, we obtained both stereoisomers of 2-benzyloxycyclobutane-α-amino acid [c_4Ser(OBn)], serine analogues **10f** and **11f**, by acid hydrolysis of **8f** and **9f** (Table 2, entries 6 and 7), respectively. These amino acids can be regarded as protected serine analogues with a conformational restriction and were prepared for inclusion in peptides (Scheme 3). This methodology offers a considerable advantage on those previously described ones for the preparation of c_4Ser.[13]

Scheme 3. Synthesis of c_4Ser(OBn) **10f** and **11f**

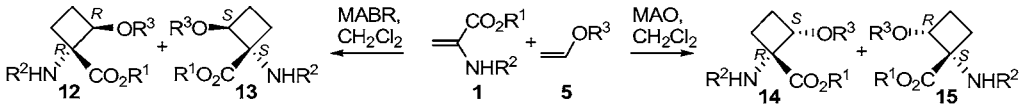


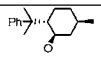
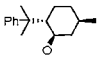
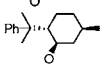
We attempted the asymmetric version of this formal [2 + 2] reaction using various chiral auxiliaries and testing several conditions (Table 3). The best results with respect to diastereoselectivity corresponded to the reaction of olefin **1a** with (−)-(1*R*,2*S*)-2-phenylcyclohexyl vinyl ether (**5i**), giving a single diastereomer (**12ai**) in 45% yield with MABR and exclusively **15ai** in 62% yield with MAO (Table 3, entries 3 and 9). The absolute configurations were determined by X-ray diffraction[7] and NOE experiments, showing a (1*R*,2*R*)-configuration for the cyclobutane ring in **12ai** and a (1*S*,2*R*)-configuration for the cyclobutane ring in **15ai**. With the aim of increasing the yield, we used the chiral donor olefin (−)-(1*R*,2*S*,5*R*)-8-phenylmenthyl vinyl ether (**5j**) with the acceptor olefin **1a**, obtaining a 70% yield with MABR, but now with a lower diastereomeric ratio (**12aj**/**13aj** = 76:24) (Table 3, entry 4). To attempt the diastereoselectivity inversion, obviously, we could obtain the cyclobutane rings of (1*S*,2*S*)- and (1*R*,2*S*)-configurations using (+)-(1*S*,2*R*)-2-phenylcyclohexanol as a chiral auxiliary. Nevertheless, and with the aim to introduce chirality into the acceptor olefin, we carried out the reaction of **5a** with (−)-(1*R*,2*S*,5*R*)-8-phenylmenthyl 2-acetamidoacrylate **1c**, which gave **12ca**/**13ca** = 15:85 but with a low yield (13%). The absolute configuration was again determined by X-ray analysis[7] of

(12) Taking into account that this type of [2 + 2] reaction is driven by HOMO−donor olefin and LUMO−acceptor olefin: (a) Scheeren, H. W.; van Rossum, A. J. R.; Nivard, R. J. F. *Tetrahedron* **1983**, *39*, 1345. (b) Srisiri, W.; Padias, A. B.; Hall, H. K., Jr. *J. Org. Chem.* **1994**, *59*, 5424.

(13) Avenoza, A.; Busto, J. H.; Canal, N.; Peregrina, J. M. *J. Org. Chem.* **2005**, *70*, 330.

Table 3. Asymmetric Michael−Aldol Reaction



entry	acceptor olefin	donor olefin	OR^1	R^2	OR^3	time (h)	yield (%) [a]	products	ratio [a]
1 [b]	**1c**	**5a**		COMe	OEt	6	13	**12ca/13ca**	15/85
2 [b]	**1d**	**5a**		COMe	OEt	4	30	**12da/13da**	40/60
3 [d]	**1a**	**5i**	OMe	COMe		15	45	**12ai/13ai**	>98/2
4 [c]	**1a**	**5j**	OMe	COMe		21	70	**12aj/13aj**	76/24
5 [c]	**1a**	**5k**	OMe	COMe		15	55	**12ak/13ak**	60/40
6 [c]	**1b**	**5i**	OMe	$COCF_3$		17	18	**12bi/13bi**	>98/2
7 [c]	**1b**	**5j**	OMe	$COCF_3$		16	56	**12bj/13bj**	80/20
8 [c]	**1b**	**5k**	OMe	$COCF_3$		18	30	**12bk/13bk**	60/40
9 [e]	**1a**	**5i**	OMe	COMe		20	62	**14ai/15ai**	>2/98

[a] Yield and ratio measured by ^{1}H NMR spectroscopy of the H-2 proton signal after column chromatography. [b] All reactions were carried out with 2.0 equiv of MABR and 5.0 equiv of donor olefin at room temperature. [c] All reactions were carried out with 2.0 equiv of MABR and 3.0 equiv of donor olefin at room temperature, except entries 6−8, which were carried out at −20 °C. [d] Reaction was carried out with 2.0 equiv of MABR and 10.0 (5.0 + 5.0) equiv of donor olefin at room temperature. [e] Reaction was carried out with 4 mL of MAO for 0.7 mmol of **1a** and 5.0 equiv of donor olefin at room temperature.

the major compound (**13ca**), which showed a (1*S*,2*S*)-configuration for the cyclobutane ring (Table 3, entry 1).

In conclusion, we have developed a formal [2 + 2] cycloaddition reaction of 2-amidoacrylates with donor olefins, and the stereoselectivity of this reaction can be modulated by the use of sterically hindered aluminum aryloxides or methylaluminoxane as Lewis acids. The reaction was extended to include several monosubstituted olefins and was applied to the synthesis of both stereoisomers of 2-benzyloxycyclobutane-α-amino acid, which are protected serine analogues c_4Ser(OBn). The asymmetric version was accomplished using chiral auxiliaries supported in an acceptor olefin or a donor olefin, thus modulating the selectivity obtained in the stereogenic centers of the cyclobutane ring. Further theoretical studies in order to study a tentative reaction mechanism for the diastereoselective formation of the cycloadducts are in progress.

Acknowledgment. We thank the Ministerio de Ciencia y Tecnología (Ramon y Cajal contract of J.H.B.), the Universidad de La Rioja (Project API-04/02), and the Gobierno de La Rioja (doctoral fellowships of N.C. and M.P.-F.).

Note Added in Proof: In the course of the revision process of our manuscript, Prof. H. Yamamoto has published (*Org. Lett.* **2005**, *7*, 3127) a very interesting paper on diastereoselective [2 + 2] cyclizations catalyzed by bulky aluminum catalysts.

Supporting Information Available: Experimental procedures, spectroscopic data, and CIF files for **7a**, **8e**, **8h**, **12ai**, and **13ca**. This material is available free of charge via the Internet at http://pubs.acs.org.

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