Titanium Isopropoxide as Efficient Catalyst for the Aza-Baylis−Hillman Reaction. Selective Formation of α-Methylene-β-amino Acid Derivatives

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The direct formation of α-methylene-β-amino acid derivatives is achieved using the aza version of the Baylis−Hillman protocol. The products are readily formed in a three-component one-pot reaction between arylaldehydes, sulfonamides, and α,β-unsaturated carbonyl compounds. The reaction is efficiently catalyzed by titanium isopropoxide and 2-hydroxyquinuclidine in the presence of molecular sieves. The protocol allows for structural variation of the substrates, tolerating electron-poor and electron-rich arylaldehydes and various Michael acceptors.

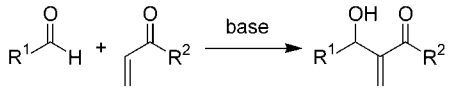
Introduction

Mild and selective carbon−carbon bond formations represent one of the major challenges in organic synthesis, and the frequent use of such transformations in, for instance, the total synthesis of complex natural products emphasizes the importance of developing useful and general protocols for this class of reactions. From the same perspective, atom-economic reactions become more and more a need and a requirement.[1]

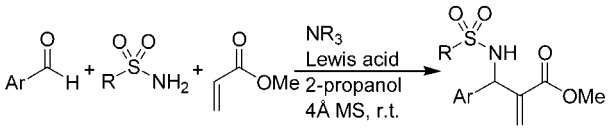
A carbon−carbon bond forming reaction which fulfills the above criteria is the Baylis-Hillman reaction.[2,3] In this transformation, Michael acceptors are coupled with aldehydes to form highly functionalized α-methylene-β-hydroxy carbonyl compounds (Scheme 1).

The related α-methylene-β-amino carbonyls are typically prepared via amine substitution of the alcohol functionality in Baylis-Hillman adducts.[4] This reaction require a two-step procedure and is often accompanied by deleterious side-reactions, e.g. S_N2'-substitution or Michael addition, leading to the formation of regioisomers.[4b,c,5] An attractive alternative route toward the formation of α-methylene-β-amino acid derivatives goes via the *aza* version of the Baylis-Hillman reaction, i.e., employing an imine as electrophile instead of an aldehyde.[6] This protocol produces the desired compounds in a single reaction step, although the aldimine usually needs to be preformed and isolated prior to the coupling reaction. In agreement with observations made on the regular Baylis-Hillman system,[2a,c] these reactions tend to be very substrate dependent and a number of different reaction conditions have been reported.[6]

Scheme 1



Scheme 2. Three-Component Aza-Baylis−Hillman Reaction Illustrated with Methyl Acrylate as Michael Acceptor



We have recently reported on an efficient and selective one-pot three-component procedure for the formation of α-methylene-β-amino acid derivatives using the aza-Baylis-Hillman protocol (Scheme 2).[7]

In accordance with the general observations on the original version of the reaction,[2,3] we found that nucleophilic, nonsterically hindered tertiary amines showed best activity as catalysts. Furthermore, we observed that the addition of $La(OTf)_3$ and molecular sieves dramatically improved chemical yields and reaction rates. These conditions turned out to be quite general, and a number of α-methylene-β-amino acid derivatives were selectively prepared employing this protocol.

The mechanism for the Baylis-Hillman reaction was already proposed by Morita[3a] in the first report of the reaction and later sustained by other studies.[2b,8,9] We have no reason to believe there are any major changes going to the aza version of the reaction. Hence, we

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(1) Trost, B. M. *Science* **1991**, *254*, 1471.

(2) (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (b) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653. (c) Ciganek, E. *Organic Reactions*, **1997**, *51*, 201.

(3) (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn*. **1968**, *41*, 2815. (b) Baylis, A. B.; Hillman, M. E. D. German patent 2155113, **1972** (*Chem. Abstr.* **1972**, *77*, 34174q).

(4) (a) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Gong, J. H. *Synlett* **2002**, *1*, 173. (b) Drewes, S. E.; Horn, M. M.; Ramesar, N. *Synth. Commun.* **2000**, *30*, 1045. (c) Takagi, M.; Yamamoto, K. *Chem. Lett*. **1989**, 2123. (d) Brown, J. M.; James, A. P.; Prior, L. M. *Tetrahedron Lett*. **1987**, *28*, 2179.

(5) (a) Kulkarni, B. A.; Ganesan, A. *J. Comb. Chem*. **1999**, *1*, 373. (b) Kundu, M. K.; Bhat, S. V. *Synth. Commun*. **1999**, *29*, 93. (c) Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett*. **1999**, *40*, 981. (d) Foucaud, A.; El Guemmout, F. *Bull. Soc. Chim. Fr*. **1989**, 403.

(6) (a) Perlmutter, P.; Teo, C. C. *Tetrahedron Lett*. **1984**, *25*, 5951. (b) Bertenshaw, S.; Kahn, M. *Tetrahedron Lett*. **1989**, *30*, 2731. (c) Cyrener, J.; Burger, K. *Monatsh. Chem*. **1994**, *125*, 1279. (d) Campi, E. M.; Holmes, A.; Perlmutter, P.; Teo, C. C. *Aust. J. Chem*. **1995**, *48*, 1535. (e) Génisson, Y.; Massardier, C.; Gautier-Luneau, I.; Greene, A. E. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 2869. (f) Richter, H.; Jung, G. *Tetrahedron Lett*. **1998**, *39*, 2729. (g) Shi, M.; Xu, Y.-M. *Chem. Commun*. **2001**, 1876.

(7) Balan, D.; Adolfsson, H. *J. Org. Chem* **2001**, *66 (19)*, 6498.

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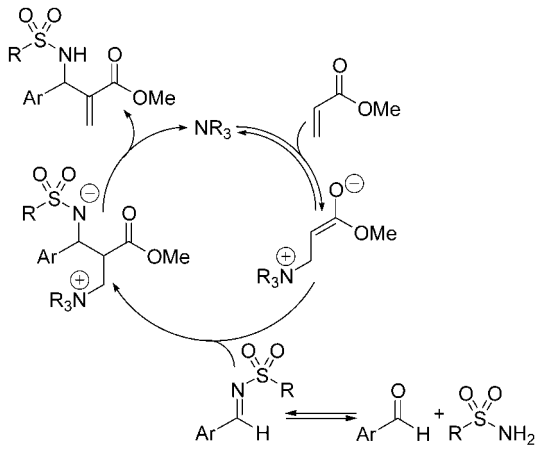
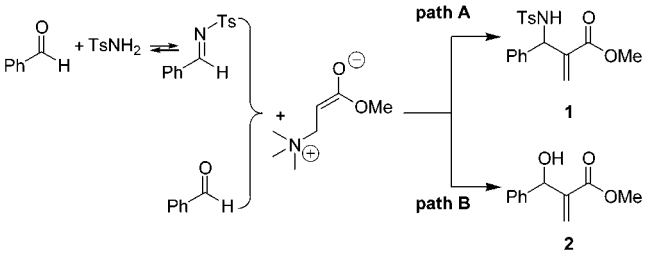
Scheme 3. Postulated Mechanism for the Aza-Baylis−Hillman Reaction



Scheme 4. Model System for the Study of the Three-Component Aza-Baylis−Hillman Reaction[a]



[a] Path A represents the desired process. Path B illustrates the competing side reaction.

presume the mechanism for the aza approach to be similar to the one originally proposed, but translated for an aldimine instead of an aldehyde (Scheme 3).

One of the major drawbacks with the aza-Baylis-Hillman reaction, and the parent reaction, is the long reaction times typically required to obtain synthetically useful yields of the desired adducts. The modifications previously reported by us somewhat improved the system, but reaction times on the order of one to 3 days were still necessary for high conversion to the aza adducts. In this context, we focused our investigations toward a fast, selective and general protocol for the formation of α-methylene-*β*-amino carbonyls using a three-component system. Herein we report on the important factors leading to high reaction rates and good chemoselectivity in the three-component aza-Baylis-Hillman reaction.

Results and Discussion

In our previous studies on the one-pot three-component aza-Balis-Hillman reaction we observed that reaction rates were affected by various catalysts (Lewis acids and bases) and additives (molecular sieves). This led us to investigate what factors could further accelerate the system. As a model for the optimization we chose to study the reaction between *p*-toluenesulfonamide, benzaldehyde and methyl acrylate, in the presence of a base catalyst (Scheme 4). As illustrated in Scheme 4, there are two competing reaction paths in this three-component system. The enolate, formed by Michael addition of the tertiary amine catalyst on the acrylate, can attack either the in situ formed aldimine (path **A**) or the aldehyde (path **B**). Since the equilibrium in the initial process (aldimine formation) is not completely in favor of the aldimine, there will always be aldehyde present in the reaction mixture (vide infra). The aldehyde will, thus, compete with the aldimine in the Baylis-Hillman step and this can lead to low selectivity of the process. The slower the imine formation occurs, or the more active the aldehyde is, the more alcohol adduct **2** will form in parallel with the desired amine product **1**. Therefore, one of the important aspects of this protocol, next to the achievement of high chemical yield, was to control the chemoselectivity of the reaction.

We have previously reported that diazabicyclo[2.2.2]-octane (DABCO) catalyzed the formation of the aza adduct, although with poor chemoselectivity and rather long reaction time.[7] Aggarwal et al have recently shown that a significant rate improvement could be achieved in the classical Baylis-Hillman reaction by the introduction of a Lewis acid catalyst together with a stoichiometric amount of DABCO.[10,11] We employed this strategy in the aza version of the reaction, performing the reaction in THF, and observed an increase in conversion to adduct **1** by the addition of 2 mol % of $La(OTf)_3$ and only 15 mol % of the base. The poor chemoselectivity obtained was attributed to slow formation of the imine. To increase the rate of the latter reaction, and thereby push the equilibrium toward the imine side, molecular sieves (4 Å) were added to trap water formed during this step. This had a dramatic influence on both conversion and chemoselectivity, resulting in almost exclusive formation of the desired amine-adduct **1** in 79% yield after 24 h. A further reduction of the amount of base (10 mol %) resulted in lower chemical yield (69%), although the chemoselectivity was unaffected and remained high. The tertiary amine catalyst is known to coordinate to the Lewis acidic metal center, which in terms results in a lower amount of free DABCO available for the Baylis-Hillman step.[10] Thus, an excess of the base catalyst over the Lewis acid was found to be a necessary prerequisite for a good turnover in the reaction.

We then examined the influence of the solvent on the reaction. Previous studies on the classical Baylis-Hillman reaction have shown that a catalytic amount of alcohol, either methanol[12] or 2-propanol,[6b] as well as diol or triol ligands when using Lewis acids,[10] had a positive influence on the reaction rate. This was believed to arise from a beneficial hydrogen bond formation between the alcohol moiety and the enolate formed by the Michael attack of the tertiary amine on the acrylate. Stabilization via hydrogen bonding was suggested to result in a higher concentration of the enolate, which directly was translated into better chemical yields. With this in mind, we changed the solvent from THF to 2-propanol, but no significant improvement was observed. Only small changes in conversion were obtained upon heating the reaction mixture to 40 °C, or when the reaction was performed in refluxing 2-propanol. In fact, using the latter conditions resulted in a lower yield of adduct **1**. These results

(8) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 795.

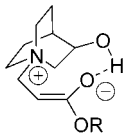
(9) Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett*, **1986**, *27*, 5007.

(10) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183.

(11) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311.

(12) (a) Ameer, F.; Drewes, S. E.; Freese, S.; Kaye, P. T. *Synth. Commun.* **1988**, *18*, 495. (b) Grob; C. A. *Helv. Chim. Acta* **1985**, *68*, 882.

together with the high volatility of the acrylate and its tendency to polymerize at elevated temperatures suggested that further investigations were to be performed at room temperature. Regarding the choice of nucleophilic base, tertiary amines such as DABCO and 3-hydroxyquinuclidine (3-HQD) have proven to be efficient catalysts for the classical Baylis-Hillman reaction.[13] In fact, 3-HQD was regarded to be superior to DABCO as a catalyst due to a favorable stabilization of the zwitterionic enolate intermediate by formation of intramolecular hydrogen bonds.



In our hands, the use of 3-HQD resulted in a higher reaction rate, although the final conversion was not affected (86% of amino-adduct **1** formed in 24 h instead of 48 h using DABCO). A minor decrease in chemoselectivity was also observed. Some of the other catalysts previously employed in the Baylis-Hillman reaction, e.g. DBU,[11] DMAP[11] or PPh_3,[6b] gave poor results when applied in the aza-Baylis-Hillman protocol. Using cinchonidine as the base catalyst in the reaction resulted 35% of **1** in 6 days.[14] The poor reactivity of the alkaloid base can be attributed to the steric bulkiness present in the vicinity of the nucleophilic quinuclidine part of the molecule, which severely hindered the attack on the acrylate.[15]

We then focused on determining the influence of various Lewis acids in the aza-Baylis-Hillman reaction.[16] To the model system used above, i.e., methyl acrylate, benzaldehyde and tosylamide, were added 15 mol % of 3-HQD and 2 mol % of a Lewis acid. The reactions were performed in 2-propanol, at ambient temperature and the results of using a number of standard Lewis acids are presented in Table 1.

For better comparison on the activity of different Lewis acids, the reactions were monitored after 11 h. At this time we anticipated the reactions not to be fully completed, and a more accurate evaluation of the results would thus be possible.

Although small differences were observed using various Lewis acids, $Sc(OTf)_3$, $Yb(OTf)_3$ and $Ti(OiPr)_4$ proved to be slightly more efficient in catalyzing the reaction, both in terms of yield and selectivity. In a closer study to gain further insight into what influences these Lewis acids impose on the system, we monitored the reaction profiles over time with respect to the yield of the amine-adduct **1** (Figure 1). In addition to the above Lewis acids, $Cu(OTf)_2$ was included in the study since very high

Table 1. Lewis Acid Screening for the Aza Version of the Baylis−Hillman Reaction[a]

entry	Lewis acid	**1**[b] (%)	**2**[b] (%)
1	$La(OTf)_3$	65	traces
2	$Sc(OTf)_3$	72	traces
3	$Yb(OTf)_3$	73	6
4	$BF_3{\cdot}Et_2O$	55	5
5	$Cu(OTf)_2$	63	-
6	$Y(OTf)_3$	65	4
7	$Ti(OiPr)_4$	83	-
8	$AlCl_3$	60	6
9	$CeCl_3$	52	4
10	$FeCl_3$	65	4
11	$Zr(O\text{-}t\text{-}Bu)_4$	65	5

[a] Reaction conditions: Benzaldehyde, *p*-toluenesulfonamide, and methyl acrylate (1:1:1.1), 3-hydroxyquinuclidine (0.15 equiv), Lewis acid (0.02 equiv), and molecular sieves (4 Å, 200 mg/mmol substrate) in 2-propanol (substrate concentration 2 M) at ambient temperature. Reaction time: 11 h. [b] Yields determined by ^1H NMR with benzyl alcohol as internal standard.

chemoselectivity was obtained when using this catalyst in the reaction (Table 1, entry 5). The four Lewis acid catalysts were compared to $La(OTf)_3$ and to the blank reaction (i.e. the reaction not containing any Lewis acid).

The first observation from the plots in Figure 1 shows upon a rather substantial rate difference between reactions performed using either 3-HQD (Figure 1.a) or DABCO (Figure 1.b) as the nucleophilic base. The reaction profiles in the latter case − reactions over 24 h − were similar to the ones obtained during the first 8−10 h using 3-HQD as the base catalyst. This is an incontestable evidence that 3-HQD is a much more efficient catalyst for the reaction. Furthermore, the influence of different Lewis acids was more evident when 3-HQD was used. The observed yields range over more than 25% after 10 h depending on which Lewis acid was employed, whereas in the case of DABCO, the different Lewis acids appeared to have much less influence on the reaction. Independently with regard to which base was employed, $Ti(OiPr)_4$ proved to be the superior Lewis acid, showing high activity in catalyzing the in situ imine formation, and the following Baylis-Hillman step. Combined with 3-HQD, $Ti(OiPr)_4$ gave very good yield and selectivity of the amine-adduct in significantly shorter reaction time than what was observed using the other Lewis acids. When using $Cu(OTf)_2$ as Lewis acid, the shape of the reaction profile obtained differed quite substantially compared to what was observed using the other Lewis acids. This effect was most evident in the reaction performed using 3-HQD as base. In the beginning of the reaction, a delay time was observed where the product formation was slower than in the reaction performed without any Lewis acid. This can find an explanation in the high affinity of copper for nitrogen donor ligands, which will give rise to a strong coordination of the base catalyst to the metal-ion. The low active concentration of base thereby obtained would effectively reduce the rate of the Baylis-Hillman step. All the other Lewis acids used in the study are typically oxophilic, which explains why no such phenomena were observed in those reactions. A further explanation can be found when considering the rate of the in situ imine formation (Figure 2).

The plots in Figure 2 show upon an interesting effect regarding the three-component system. In most of the cases, benzaldehyde was found to be in excess over the in situ formed imine throughout the entire reaction. The use of copper triflate and titanium isopropoxide respec-

(13) (a) Drewes, S. E.; Freese, S. D.; Emslie, N. D.; Roos, H. P. *Synth. Commun.* **1988**, *18*, 1565. (b) Bailey, M.; Markó, I. E.; Ollis, W. D.; Rasmussen, P. R. *Tetrahedron Lett.* **1990**, *31 (31)*, 4509. (c) Bode, M. L.; Kaye, P. T. *Tetrahedron Lett.* **1991**, *32 (40)*, 5611.

(14) Adduct **1** was formed in 40% enantiomeric excess. For diastereoselective Baylis Hillman reactions on aldimines, see; (a) Aggarwal. V. K.; Martin Castro, A. M.; Mereu, A.; Adams, H. *Tetrahedron Lett.* **2002**, *43*, 1577. (b) Kündig, E. P.; Xu, L. H.; Schnell, B. *Synlett* **1994**, 413. (c) Kündig, E. P.; Xu, L. H.; Romanens, P.; Bernardinelli, G. *Tetrahedron Lett.* **1993**, *34*, 7049.

(15) Improvements in catalytic activity and stereoselectivity in the classic Baylis-Hillman reaction were obtained using a modified cinchona alkaloid. For details, see; Iwabuchi, Y.; Nakatani, M.; Yokohama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

(16) For a recent classification of Lewis acid activity and selectivity in enolate additions to aldehydes and aldimines, see; Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Eur. J.* **2000**, *6*, 3491.

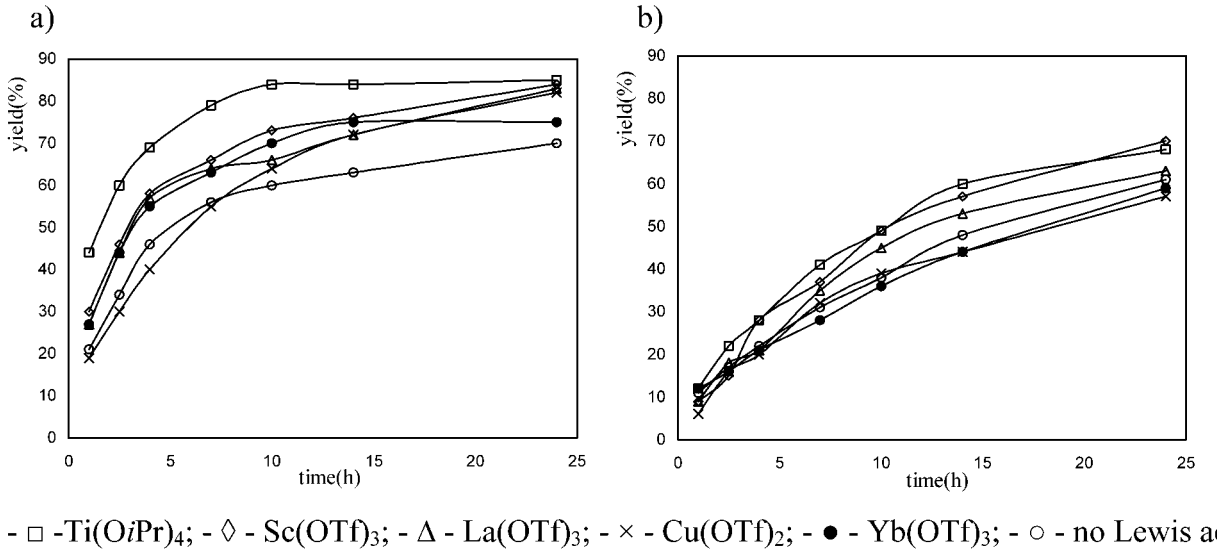


Figure 1. Reaction profiles for the aza-Baylis−Hillman reaction in the presence of different Lewis acids, using (a) 3-HQD or (b) DABCO as base.

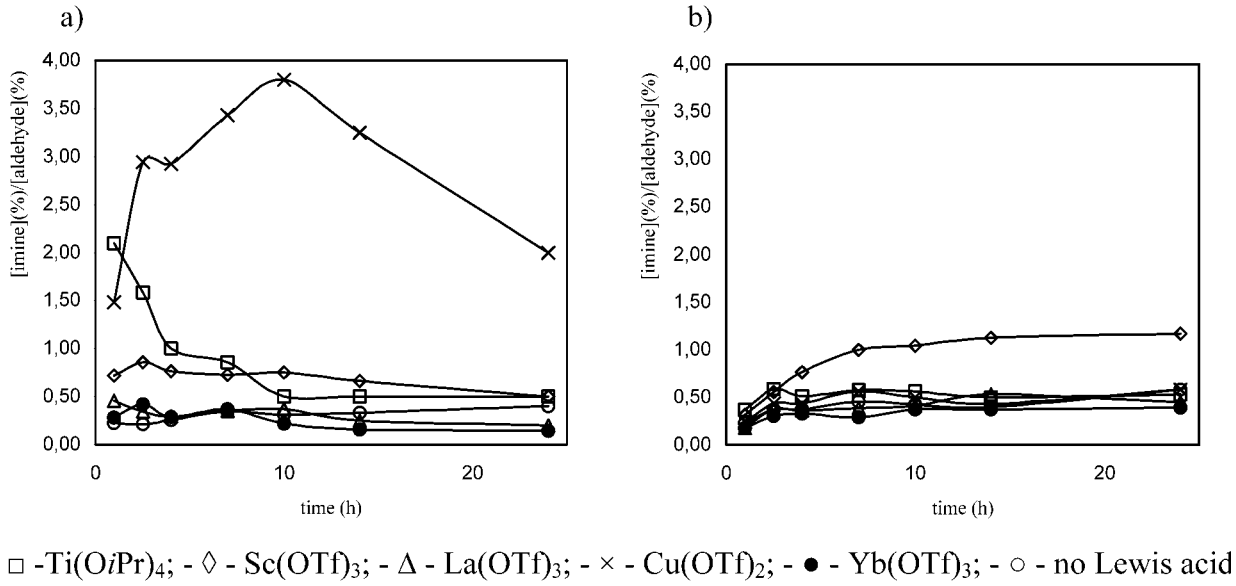
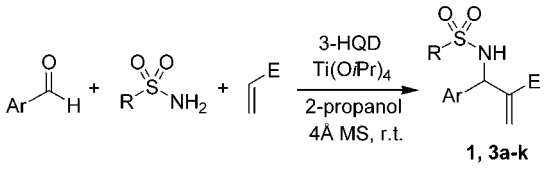


Figure 2. Imine−aldehyde ratio during the aza-Baylis−Hillman reaction in the presence of different Lewis acids, using (a) 3-HQD and (b) DABCO as base.

tively in combination with 3-HQD resulted, however, in an efficient formation of the imine already from the beginning of the reaction (Figure 2a). The excellent chemoselectivities obtained in these cases are most certainly reflected in the efficiency with which these Lewis acids catalyze the imine formation. In the case of copper triflate, the slow initial rate observed for the Baylis-Hillman step (Figure 1a) was proposed to arise from a low active concentration of base. The fact that the reaction still proceedes can then be traced to the overall high imine concentration. It is important to notice, that no such effects were observed using these Lewis acids in combination with DABCO (Figure 2.b). This further stresses the importance of choosing the proper combination of Lewis acid- and base catalysts. While the combination of copper triflate and 3-HQD most efficiently catalyzed the imine formation, titanium isopropoxide in the presence of the same base gave the best overall rate of the reaction. In the latter case, the aza-Baylis-Hillman

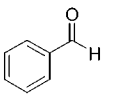
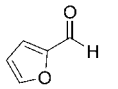
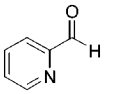
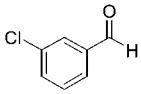
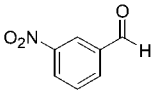
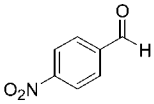
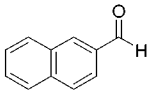
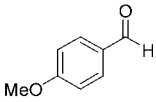
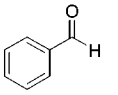
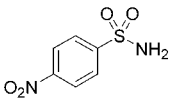
Scheme 5



reaction proved to be highly chemoselective even though considerable amounts of benzaldehyde was present in the reaction mixture next to the in situ formed imine (ratio 1:2 at low conversions, 1:1 and 2:1 during the progress of the reaction).

From the above results, we concluded that the optimized conditions for the aza-Baylis-Hillman reaction were as follows: 15 mol % of 3-hydroxyquinuclidine and 2 mol % of titanium isopropoxide as catalysts, performing the reaction at ambient temperature in 2-propanol in the presence of molecular sieves. These conditions were

Table 2. Scope of Aza-Baylis−Hillman Reaction under Optimized Conditions[a]

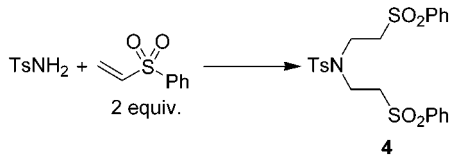
Entry	Reactants			Time	Product/Yield[b]		Selectivity[c]
	Aldehyde	Sulfonamide	Michael acceptor	(h)	amine	(%)	(%)
1				8	**1**	85	>99
2		″	″	6	**3a**	83	>99
3[d]		″	″	6	**3b**	72	92
4		″	″	6	**3c**	94	>95
5		″	″	6	**3d**	80	>95
6		″	″	14	**3e**	88	>99
7		″	″	14	**3f**	67	>99
8		″	″	14	**3g**	58	>99
9		″		24	**3h**	53	>99
10	″	″		14	**3i**	64	83
11[e]	″	″		24	**3j**	12	78
12	″			24	**3k**	77	>99

[a] Reaction conditions: aldehyde, sulfonamide, and Michael acceptor (1:1:1.1), 3-hydroxyquinuclidine (0.15 equiv), Ti(O*i*Pr)$_4$ (0.02 equiv) and molecular sieves (4 Å, 200 mg/mmol substrate) in 2-propanol (substrate concentration 2 M) at ambient temperature. [b] Isolated yields. [c] Chemoselectivity based on NMR yields, measured with benzyl alcohol as internal standard and expressed as the ratio between amine **3** and the combined two products of the reaction (amine **3** and the alcohol adduct**)**. [d] The imine was preformed during 2 h before the acrylate was added in order to improve selectivity (otherwise 80%). [e] The imine was preformed during 12 h before the Michael acceptor was added to improve selectivity (otherwise 50%, see text).

applied in the formation of a number of α-methylene-β-amino acid derivatives employing the aza version of the Baylis-Hillman protocol (Scheme 5 and Table 2). As found for the model reaction, the optimized conditions gave in general considerable shorter reaction times and better chemoselectivities, as compared to our previously reported results.[7]

Arylaldehydes substituted with electron-withdrawing groups reacted very fast giving the desired α-methylene-β-amino acid derivatives in high yields and good chemoselectivities (entries 3−6). The high selectivities obtained were very gratifying considering the fact that the side-reaction leading to the alcohol adduct also would be accelerated by electron-poor aldehydes. Arylaldehydes bearing electron-releasing groups required slightly longer reaction times to reach high conversion, although the selectivities were found to be excellent (entries 7−8). *tert*-Butyl acrylate was converted to the aza adduct in high

Scheme 6. Side Reaction Observed between Phenyl Vinyl Sulfone and *p*-Toluenesulfonamide



4

selectivity, but only with a modest chemical yield (entry 9). The increased reaction time and lower yield obtained using this substrate indicates that the reaction is sensitive to the steric hindrance imposed by the bulky *tert*-butyl ester. Acrylonitrile, a substrate normally reacting very fast under Baylis-Hillman conditions, gave a surprisingly poor yield employing the aza-Baylis-Hillman protocol (entry 10).

A plausible explanation can be found when considering the role of the Lewis acid. Since esters were reacting rather fast under these conditions, we believe that the titanium isopropoxide catalyst which is essential for the in situ formation of the imine, also plays an important role in activating the Michael acceptor. The oxophilic nature of the titanium catalyst would therefore activate the ester more than the nitrile. Phenyl vinyl sulfone proved to be an excellent Michael-acceptor, although not in the fashion we had anticipated. Instead of reacting with the basic 3-HQD producing the intermediate enolate, the vinyl sulfone underwent a 1,4-addition by the rather poor nucleophile *p*-toluenesulfonamide. The formed adduct reacted further with a second equivalent of the vinyl sulfone producing compound **4** (Scheme 6). This side-reaction could, however, be suppressed by adding the Michael acceptor after 12 h, which allowed for the preformation of the imine in the reaction mixture. The active concentration of the sulfonamide was thereby efficiently decreased and we succeeded in increasing the chemoselectivity from 50% to 78%, although the chemical yield remained rather poor.

Furthermore, the electron-poor sulfonamide, 4-nitrobenzenesulfonamide, was efficiently used as amine-source in the aza-Baylis-Hillman reaction (entry 12). The mild cleavage protocol available for this particular sulfonamide suggests a straightforward approach toward nonprotected α-methylene-*β*-amino acid derivatives.[17]

As we previously observed, and in contrast to other reports,[6h,18] *β*-substituted Michael acceptors (e.g. cyclohex-2-en-1-one) did not react to give the desired aza-Baylis-Hillman adducts. Not even under these optimized conditions did we observe anything but imine formation, thus, there was neither reaction with the cyclohex-2-en-1-one, nor alcohol adduct formation from reaction with the aldehyde.

Alifatic aldehydes did not yield any aza adducts using the above protocol. The main reason for the low reactivity observed for this class of aldehydes stem from the very slow formation of the intermediate imines.

Conclusions

Herein we have reported on an efficient, combined Lewis acid- and base-catalyzed, three component one-pot procedure for the formation of α-methylene-*β*-amino acid derivatives using a modified Baylis-Hillman protocol. In the reaction, arylaldehydes, sulfonamines and Michael acceptors were combined to form the title compounds in high yields and with good to excellent chemoselectivities. A systematic study, varying the reaction components led to the optimized conditions for the aza-Baylis-Hillman reaction. We found that the choice of Lewis acid combined with the proper base was crucial for high yield and selectivity. Although DABCO efficiently catalyzed the formation of the adducts, 3-hydroxyquinuclidine, in the presence of titanium isopropoxide as Lewis acid, was found to be the superior base catalyst. Furthermore, the addition of molecular sieves to the reaction mixture dramatically improved the yield of the aza adduct, and hence the chemoselectivity.

Experimental Section

General experimental procedure[19] for the aza version of the Baylis-Hillman reaction, exemplified for the formation of **methyl α-methylene-*β*-[(*p*-toluenesulfonyl)-amino]-3-phenylpropionate**[6d] **(1)**

In a dried flask, *p*-toluenesulfonamide (855 mg, 5 mmol) and 3-hydroxyquinuclidine (15 mol %, 0.75 mmol, 95 mg) were measured together with molecular sieves (4 Å, 900 mg). 2-Propanol (2.5 mL),[20] benzaldehyde (505 μL, 5 mmol), methyl acrylate (495 μL, 5.5 mmol) and $Ti(OiPr)_4$ (2 mol %, 0.1 mmol, 30 μL) were added and the reaction mixture was stirred for 8 h at ambient temperature. The mixture was filtered through a thin layer of Celite, which was rinsed three times with 2-propanol (10 mL). The solvent was evaporated and to the crude were added methanol (25 mL) and aqueous sulfuric acid (10 mL, 1M).[21] The solution was stirred for 1 h, then methanol was evaporated. The remaining acidic solution was diluted with water and extracted with dichloromethane (3 × 30 mL). The organic phase was then successively washed with $NaHCO_3$ (sat.), NaOH (1M), water and brine, and dried over Na_2SO_4. Evaporation of the solvent gave 1.47 g (85%) of the pure product as a white crystalline material: Mp 76−77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.61 (s, 3H), 5.31 (d, J = 8.9 Hz, 1H), 5.61 (d, J = 8.9 Hz, 1H), 5.83 (s, 1H), 6.22 (d, J = 0.7 Hz, 1H); 7.13−7.25 (m, 7H), 7.68 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.72, 52.20, 59.31, 126.64, 127.45, 127.98, 128.10, 128.80, 129.70, 137.84, 138.74, 138.81, 143.61, 165.98; MS (MALDI-TOF) (*m*/*z*) 384.071(MK^+) 368.094 (MNa^+) 346.103 (MH^+).

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Supporting Information Available: Characterization data for all compounds in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett*. **1995**, *36*, 6373.

(18) Rezgui, F.; El Gaied, M. M. *Tetrahedron Lett*. **1998**, *39*, 5965.

(19) This procedure was applied for all reactions, except in the case of 2-pyridinecarboxaldehyde, where the Michael acceptor was added 2 h later to suppress the formation of the alcohol adduct and in the case of phenyl vinyl sulfone which was added after 12 h to suppress the formation of the byproduct **4**.

(20) For solid aldehydes 2 mL of dichloromethane was added as cosolvent.

(21) The acidic workup facilitates cleavage of remaining sulfonylimine and efficiently removes the aldehyde. For reactions with low conversion, an additional stirring with sulfuric acid (1M) was repeated after the basic workup.