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A Diastereoselective Three-Component Coupling Approach to Highly Substituted Pyrrolidines

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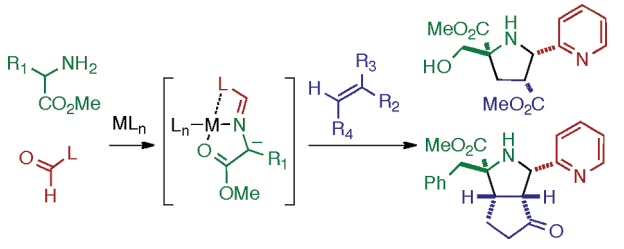

Building on the observation that metal complexation facilitates azomethine ylide formation, we report that chelating aldehydes participate in metal-templated, one-pot reactions with unprotected amino acid esters and activated olefins to provide highly substituted pyrrolidines. The high yields, broad substrate scope, excellent diastereoselectivities, functional group tolerance, and incorporation of commercially available materials in this reaction simplifies access to medicinally relevant proline derivatives.

Highly substituted proline derivatives form the core of numerous natural products and pharmaceutical candidates.[1] Examples include the recent clinical candidate GSK 625433 (**1**),[2a] the chemotherapeutic natural product spirotryprostatin (**2**),[2b] and the experimental chemotherapeutic atrasentan (**3**) (Figure 1).[2c] Consistent with their medical significance, many methods for the synthesis of these compounds have been described.[3] The most common of these involve 1,3-dipolar cycloadditions of azomethine ylides that generate pyrrolidines in a convergent and stereoselective manner.[4−6]

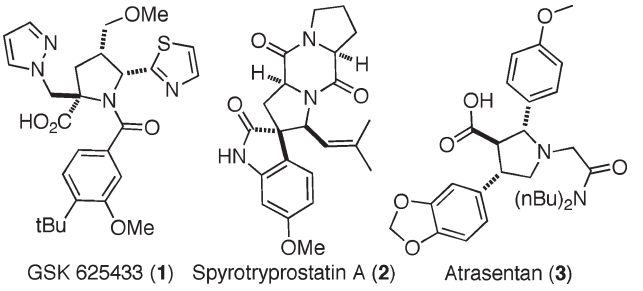

FIGURE 1. Biologically active proline derivatives.

Azomethine ylide cycloadditions are typically performed in two distinct stages that are conducted under different conditions: synthesis of ylide precursors such as Schiff bases,[4] α-silylimines,[5] and aziridines[6] and ylide formation accompanied by [3 + 2] cycloaddition. As these two-step protocols require the selective formation of ylide precursors, they exhibit inherent limitations, requiring protecting groups or multistep strategies to access pyrrolidines displaying reactive functionality such as alcohols and amines in greater than trace quantities.[4,7] Three-component couplings that

(1) (a) Enyedy, I. J.; Zaman, W. A.; Sakamuri, S.; Kozikowski, A. P.; Johnson, K. M.; Wang, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1113–1118. (b) Shih, N.-Y.; Lupo, A. T., Jr.; Aslanian, R.; Orlando, S.; Piwinski, J. J.; Green, M. J.; Ganguly, A. K.; Clark, M. A.; Tozzi, S.; Kreutner, W.; Hey, J. A. *J. Med. Chem.* **1995**, *38*, 1593–1599.

(2) (a) Slatter, M. J.; Amphlett, E. M.; Andrews, D. M.; Bravi, G.; Burton, G.; Cheasty, A. G.; Corfield, J. A.; Ellis, M. R.; Fenwick, R. H.; Fernandes, S.; Guidetti, R.; Haigh, D.; Hartley, C. D.; Howes, P. D.; Jackson, D. L; Jarvest, R. L.; Lovegrove, V. L. H.; Medhurst, K. J.; Parry, N. R.; Price, H.; Shah, P.; Singh, O. M. P.; Stocker, R.; Thommes, P.; Wilkinson, C.; Sonacott, A. *J. Med. Chem.* **2007**, *50*, 897–900. (b) Edmondson, S.; Danishefsky, S. J.; Lorenzino, L. S.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155. (c) Chippori, A. A.; Haura, E.; Rodriguez, F. A.; Boulware, D.; Kapoor, R.; Neuger, A. M.; Lush, R.; Padilla, B.; Burton, M.; Williams, C.; Simon, G.; Antonia, S.; Sullivan, D. M.; Bepler, G. *Clin. Cancer. Res.* **2008**, *14*, 1464–1469.

(4) For select examples of 1,3-dipolar cycloaddition of azomethyne ylide generated from Schiff base. (a) Zeng, W.; Chen, G.-Y.; Zhou, Y.-G.; Li, Y.-X. *J. Am. Chem. Soc.* **2007**, *129*, 750–751. (b) Tsubogo, T.; Saito, S.; Seki, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13321–13332. (c) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236–4238. (d) Allway, P; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817–5820. (e) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174–10175. (f) Yu, S.-B.; Hu, X.-P.; Deng, J.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z *Tetrahedron: Asymmetry* **2009**, *20*, 621–625. (g) Najera, C.; Retamosa, M. G.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6055–6058. (h) Cabrera, S.; Arrayas, R. G.; Matute, B. M.; Cossio, F. P.; Carretero, J. C. *Tetrahedron* **2007**, *63*, 6587–6602. (i) Zeng, W.; Zhou, Y.-G. *Tetrahedron Lett.* **2007**, *48*, 4619–4622. (j) Bicario, J. L.; Reboredo, S.; Badia, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168–5170. (k) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043–5046. (l) Wang, C.-J.; Liang, G.; Xue, Z.-Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250–17251. (m) Grigg, R.; Sridhara, V.; Suganthan, S.; Bridge, A. W. *Tetrahedron* **1995**, *51*, 295–306.

(5) (a) Vedejes, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1980**, *102*, 7993–7994. (b) Achiwa, K.; Motoyama, T.; Sekiya, M. *Chem. Pharm. Bull.* **1983**, *31*, 3939–3945. (c) Livinghouse, T.; Smith, R. *J. Org. Chem.* **1983**, *48*, 1554–1555. (d) Padwa, A.; Hoffmanns, G.; Tomas, M *Tetrahedron Lett.* **1983**, *24*, 4303–4306. (e) Tsuge, O.; Kanemasa, S.; Kuraoka, S.; Takenaka, S. *Chem. Lett.* **1984**, *279*, 281–284. (f) Komatsu, M.; Okada, H.; Akaki, T.; Oderaotoshi, Y.; Minakata, S. *Org. Lett.* **2002**, *4*, 3505–3508.

(6) (a) Heine, H. W.; Peavy, R.; Durbetaki, A. J. *J. Org. Chem.* **1966**, *31*, 3924–3927. (b) Huisgen, R.; Scheer, W.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 1753–1755. (c) Pohlhaus, P. D.; Bowman, R. K.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2294–2295.

(3) For the synthesis of pyrrolidines, see: (a) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887–2902. (b) Fujita, K.-I.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525–3528. (c) Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570–1571. (d) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747–1749. (e) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452–2453. (f) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447–6459. (g) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700–6701. (h) Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928–12929. (i) Schomaker, J. M.; Bhattacharjee, S.; Yan, J.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 1996–2003.

(7) Dondas, H. A.; Durust, Y.; Grigg, R.; Slater, M. J.; Sarker, M. A. B. *Tetrahedron* **2005**, *61*, 10667–10682.

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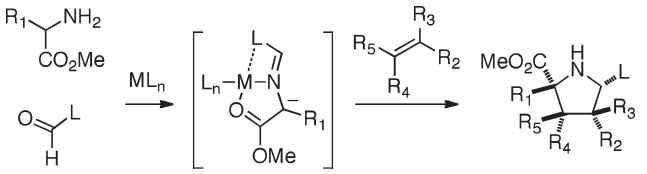
SCHEME 1. Pyrrolidine Formation via a Three-Component Azomethine Ylide [3 + 2] Cycloaddition

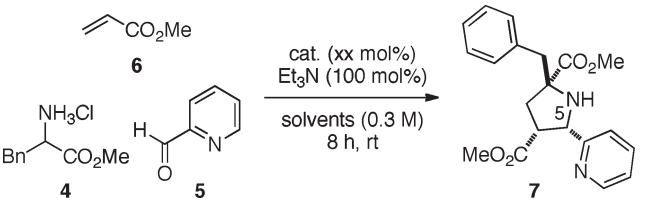


avoid these multistep protocols are desirable; however, existing methods require harsh reaction conditions, exhibit limited substrate scope, or require the use of nontrivial diazoacetate derivatives.[8−10]

Recently, we proposed the intermediate presence of azomethine ylides in picolinaldehyde/metal catalyzed amino acid racemizations.[11] Our work demonstrated that azomethine ylide formation is facilitated by metal chelation, allowing racemization to occur under mild conditions. As metal chelation stabilizes the dominant conformer of the reactant species, we hypothesized that these intermediate ylides could be used to control diastereoselectivity in 1,3-dipolar cycloadditions. We report here confirmation of our hypothesis, showing that chelating aldehydes participate in metal-catalyzed three-component coupling reactions with amino acid esters and activated olefins to generate pyrrolidines in high yields and diastereoselectivities under mild conditions (Scheme 1). Moreover, as this work appears to utilize a mechanistically distinct mode of ylide activation, it allows the efficient incorporation of amino acid esters that contain unprotected amine and alcohol functionality into azomethine ylide [3 + 2] cycloaddition reactions.[4−6]

Our rationale suggested that metal chelation could facilitate 1,3-dipole formation concurrent with Schiff base formation. In this fashion, a three-component, one-pot synthesis of pyrrolidines could be conducted. Studies began by combining phenylalanine methyl ester [Phe(OMe)] with picolinaldehyde and methyl acrylate under a variety of reaction conditions (Table 1). Our initial efforts, using metals known to be active in amine racemization,[11] provided the desired products in high yields and diastereoselectivies (Table 1, entries 2−6). Interestingly, we observed that the use of nickel salts resulted in low diastereoselectivities, providing significant quantities of the C4 epimer (Table 1, entries 7 and 8). This epimer likely stems from limited *endo*/*exo* selectivity as product epimerization was not observed under the reaction conditions. Of the metals screened, calcium(II) gave the highest yields, and further studies focused on the soluble $Ca(OTf)_2$. Reaction optimization efforts revealed limited sensitivity to the examined solvents, with comparable efficiency observed in methanol, acetonitrile and tetrahydrofuran (Table 1, entries 6, 9, and 10). $Ca(OTf)_2$ loadings as low as 2 mol % are well tolerated (Table 1; entries 6, 11, and 12);

TABLE 1. Reaction Optimization[a]



entry	cat (mol %)	solvent	yields[a] (%)	dr
1	CF_3CO_2H (10)	MeOH	< 5	ND
2	$ZnBr_2$ (10)	MeOH	80	20:1
3	$Zn(OTf)_2$ (10)	MeOH	85	20:1
4	$CuBr_2$ (10)	MeOH	60	> 20:1
5	$CaCl_2$ (10)	MeOH	> 99	> 20:1
6	$Ca(OTf)_2$ (10)	MeOH	> 99	> 20:1
7	$Ni(acac)_2$ (10)	MeOH	65	2:1
8	$NiCl_2$ (10)	MeOH	70	3:1
9	$Ca(OTf)_2$ (10)	THF	> 99	20:1
10	$Ca(OTf)_2$ (10)	MeCN	> 99	20:1
11	$Ca(OTf)_2$ (5)	MeOH	> 99	20:1
12	$Ca(OTf)_2$ (2)	MeOH	> 99	20:1
13	$Ca(OTf)_2$ (1)	MeOH	90	20:1

[a]Yields and diastereomeric ratios are based on ^{1}H NMR data of crude reaction mixtures.

however, further reductions in catalyst loading resulted in slow reactions and side product formation (Table 1, entry 13).

A variety of aldehydes bearing metal-binding substituents react well in this condensation. Altering the electronics among a series of picolinaldehydes has little effect, as exemplified by substrates bearing nitrile and methoxy substituents (Table 2, entries 1 and 2). Consistent with our hypothesis that metal chelation is critical to reactivity, reactions involving benzaldehyde and 4-pyridinecarboxaldehyde failed, whereas pyridoxal and salicylaldehyde, which contain phenolic groups ortho to the aldehyde, react smoothly (Table 2, entries 3−6). It should be noted that both salicylaldehyde and pyridoxal exhibit background reactivity in the absence of coordinating metals, presumably due to hydrogen bonding acting in place of a chelated metal catalyst. Reactions with salicylaldehyde required extended times and elevated temperatures, likely caused by limited azomethine ylide stabilization by the phenyl ring.[12] Five-membered rings exhibit similar reactivity patterns as six-membered, with thiazolyl and imidazolyl carboxaldehydes demonstrating good reactivity (Table 2, entries 7 and 8) and the poorly coordinating furanyl and pyrrolyl aldehydes proving unreactive (Table 2, entries 9 and 10). Taken as a whole, our data demonstrates the importance of metal chelation for reactivity, and the significance of functionality likely to assist in stabilizing ylide formation.

Reactions of amino acid esters demonstrated the functional group tolerance of this reaction. Unprotected alcohols and amines performed well, as seen in examples of Ser(OMe), Tyr(OMe), Trp(OMe), and Lys(OMe) (Table 3, entries 2, 3, 5, and 11). It should be noted that Ser(OMe) required higher catalyst loadings, likely due to metal sequestration by the starting material. Sterically demanding side chains are less well tolerated, with branched substrates such as valine exhibiting no reactivity in methanol, requiring acetonitrile

(8) (a) Coldham, I.; Jana, S.; Watson, L.; Martin, N. *Org. Biomol. Chem.* **2009**, *7*, 1674–1679. (b) Karthikeyan, K.; Kumar, R. S.; Muralidharan, D.; Perumal, P. T. *Tetrahedron Lett.* **2009**, *50*, 7175–7179.

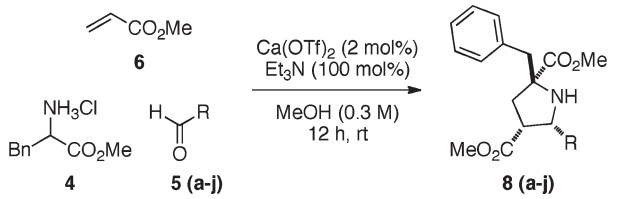
(9) (a) Garner, P.; Kaniskan, H. U. *J. Org. Chem.* **2005**, *70*, 10868–10871. (b) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-G. *J. Am. Chem. Soc.* **2008**, *130*, 5652–5653. (c) Liu, Y.-K.; Liu, H.; Du, W.; Yue, L.; Chen, Y.-C. *Chem.—Eur. J.* **2008**, *14*, 9873–9877.

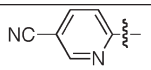
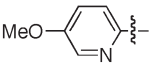
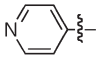
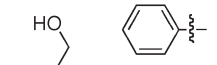
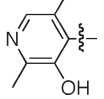
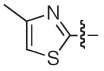
(10) (a) Galliford, C. V.; Beenen, M. A.; Nguyen, S. T.; Scheidt, K. A. *Org. Lett.* **2003**, *5*, 3487–3490. (b) Xu, H.-W.; Li, G.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2005**, *7*, 5349–5352.

(11) Felten, A.; Zhu, G.; Aron, Z. D. *Org. Lett.* **2010**, *12*, 1916–1919.

(12) Ikawa, M.; Snell, E. E. *J. Am. Chem. Soc.* **1954**, *76*, 653–655.

TABLE 2. Reaction with Different Aldehydes[a]



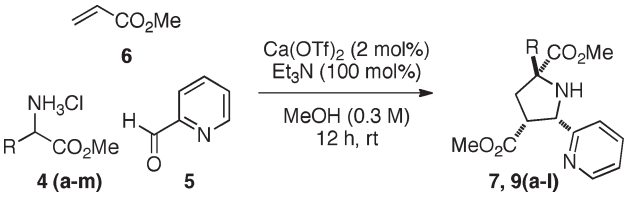
entry	R	product	yields (%)[a]	dr[b]
1		**8a**	92	>20:1
2		**8b**	85	>20:1
3		**8c**	trace	ND
4		**8d**	trace	ND
5		**8e**	87	~20:1
6[c]		**8f**	50	>20:1
7		**8g**	91	>20:1
8		**8h**	87	>20:1
9		**8i**	trace	ND
10		**8j**	trace	ND

[a]Yields reported are isolated yields. [b]Diastereomeric ratios were calculated on the basis of ^{1}H NMR data of crude reaction mixtures. [c]Reactions were conducted at 60 °C for 2 days.

for good reactivity, and neopentyl substrates such as *tert*-leucine failing to react under any conditions examined (Table 3, entries 8 and 10). Unprotected thiols such as Cys(OMe) are not tolerated due to side reactions with the starting methyl acrylate (Table 3, entry 13).

Substituted dipolarophiles react efficiently in this transformation, although they require higher catalyst loadings (Table 4, dipolarophile substituents shown in blue). The reaction works well with olefins substituted with a variety of electron-withdrawing groups including esters (**10c**−**f**), imides (**10g**), ketones (**10a**,**b**) and nitriles (**10h**). However, styrene is unreactive, suggesting that the cycloaddition requires an electron-poor dipolarophile. Reactions with acrylonitrile gave mixtures of C4 epimers that failed to exchange under the reaction conditions (**10h**), suggesting that the lack of diastereoselectivity stems from poor *endo*/*exo* selectivity. α,α-Disubstituted dipolarophiles such as methyl methacrylate provide direct access to pyrrolidines containing two quaternary carbons (**10c**). Reactions with *cis* 1,2-disubstituted dipolarophiles provide efficient access to pyrrolidines that are fully substituted on a single face (**10a**, **10b**, **10d**, and **10g**).

TABLE 3. Reaction with Different Amino Acid Esters[a]



entry	amino acid	product	yields[a] (%)	dr[b]
1	Phe(OMe)	**7**	98	> 20:1
2	Tyr(OMe)	**9a**	97	> 20:1
3	Ser(OMe)	**9b**	82[c]	> 20:1
4	Leu(OMe)	**9c**	94	> 20:1
5	Trp(OMe)	**9d**	83	> 20:1
6	Met(OMe)	**9e**	98	> 20:1
7	Ala(OMe)	**9f**	74	> 20:1
8	Val(OMe)	**9g**	88[d]	> 20:1
9	Gly(OMe)	**9h**	76	> 20:1
10	*t*-Leu(OMe)	**9i**	trace[d]	N/A
11	Lys(OMe)	**9j**	95[c,e]	~20:1
12	Phe(OtBu)	**9k**	98	> 20:1
13	Cys(OMe)	**9l**	trace	N/A

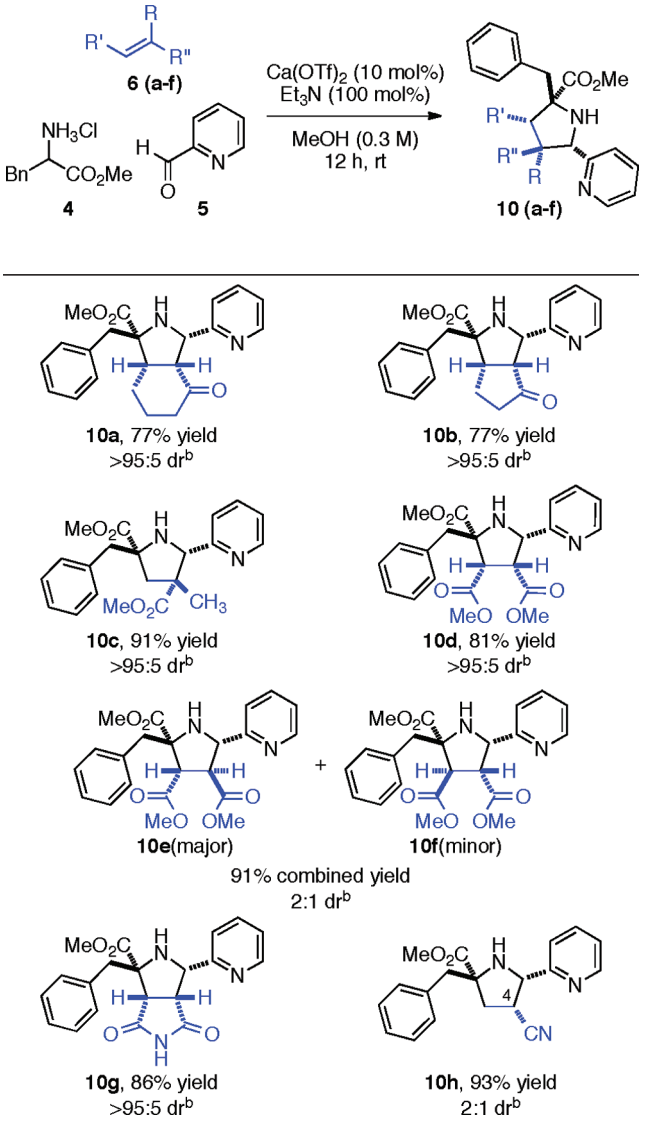
[a]Yields reported are isolated yield. [b]Diastereomeric ratios were calculated on the basis of ^{1}H NMR data of crude reaction mixtures. [c]Reactions were conducted with 10 mol % of catalyst. [d]Reactions used MeCN as solvent. [e]Yield based on ^{1}H NMR data of crude reaction mixtures.

Notably, reactions of the *trans*-substituted dimethyl fumarate gave poor diastereoselectivities, providing a 2:1 mixture of **10e** and **10f**, consistent with a lack of differentiation between *endo* and *exo* approaches.

Based on our studies, these transformations are highly regioselective, suggesting either a stepwise Micheal/Mannich reaction or a polarized asynchronous concerted [3 + 2] cycloaddition. The lack of stereochemical scrambling in reactions of dimethyl maleate (**10d**, Table 4) and dimethyl fumarate (**10e** and **10f**, Table 4) suggests that the cycloadditions occur in a concerted manner, ruling out the first possibility. Analysis of the product distribution reveals that the regioselectivity of the reaction is consistent with polarization of the azomethine ylide intermediate with higher electron density residing adjacent to the carboxylate functionality, likely due to the contribution of the enolate resonance structure shown (top resonance structure of **11**, Scheme 2). The polarization of ylide **11** would result in a higher orbital coefficient for the HOMO at this enolate carbon, resulting in preferential interactions with the larger LUMO orbital coefficient at the β-carbon of polarized dipolarophiles such as acrylate **6** to provide the observed regioselectivity.

These transformations are also highly stereoselective, with the only observed diastereoisomers stemming from the rare occurrence of incomplete *endo* selectivity. The syn relationship between the C2 carboxylate and the chelating group at C5 is consistent with chelation of the calcium enolate to both the imine and heterocycle nitrogens, interactions likely to further stabilize the deprotonated ylide intermediate.[11] This chelation may act as a template, controlling the stereochemistry of the 1,3-dipole, and thus the stereochemistry of the final product (Scheme 2). Further studies to understand the relevance of this proposed mechanism are underway.

TABLE 4. Reaction with Different Dipolarophiles[a]

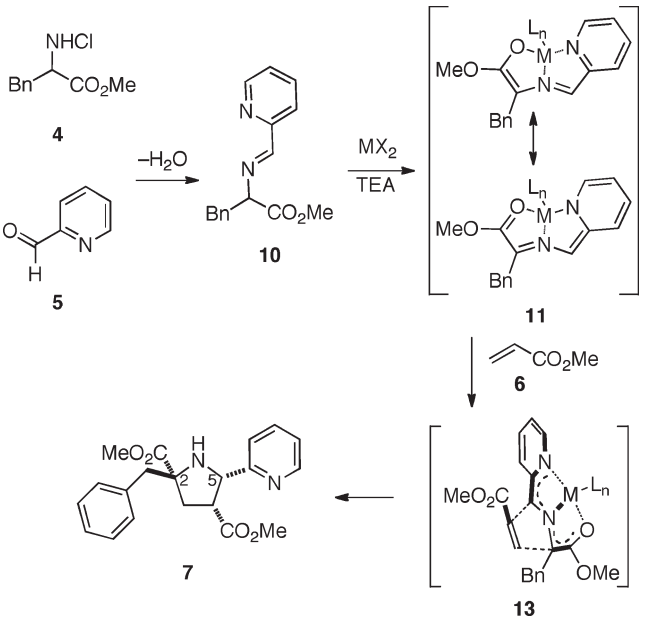


[a]Yields reported are isolated yields. [b]Diastereomeric ratios were calculated on the basis of ^{1}H NMR data of crude reaction mixtures.

In conclusion, we have developed a high yielding and diastereoselective one-pot synthesis of tri- and tetra-substituted pyrrolidines from simple and readily available starting materials. This work demonstrates the viability of metal chelation to promote the formation and use of azomethine ylides in highly selective [3 + 2] cycloadditions. These efforts provide a mild, one-step, three-component pyrrolidine synthesis that works well with a variety of simple amino acid esters. As this chemistry uses low loadings of inexpensive metals with limited toxicity,[13] tolerates a variety of solvents and is efficient in the presence of reactive functional groups, we feel that it is an attractive alternative to existing synthetic methods. Efforts toward enantioselective variants are currently underway.

(13) Calcium Trifluoromethanesulfonate; MSDS AA40134−18.asp; ChemCAS: March 15, 2005. http://www.chemcas.org/chemical/msds/cas/AA0_4/AA40134-18.asp

SCHEME 2. Proposed Path of the Reaction



Experimental Section

General Procedure. Esters of amino acids (1.0 equiv) are weighed in a clean 4 mL glass vial and dissolved in methanol (0.3 M), unless otherwise indicated. To this solution, triethylamine (1.0 equiv), aldehyde (1.0 equiv), olefin (1.2 equiv), and $Ca(OTf)_2$ (0.02 equiv, unless otherwise indicated) are added. The vial is capped and placed in a shaker for the appropriate time. Crude reactions are concentrated in vacuo and purified with flash silica column chromatography.

Representative Cycloaddition: Formation of (2*S*,4*R*,5*S*)- and (2*R*,4*S*,5*R*)-Dimethyl 2-Benzyl-5-(pyridin-2-yl)pyrrolidine-2,4-dicarboxylate (7). Phenylalanine methyl ester hydrochloride (108 mg, 0.500 mmol), triethylamine (70.0 μL, 0.500 mmol), pyridine-2-carboxaldehyde (47.0 μL, 0.500 mmol), methyl acrylate (54.0 μL, 0.600 mmol), and $Ca(OTf)_2$ (3.4 mg, 0.010 mmol) were dissolved in methanol (1.50 mL) and maintained at rt for 8 h. Following chromatography (SiO_2, ethyl acetate/hexanes 40:60, R_f = 0.4), (2*S*,4*R*,5*S*)-dimethyl 2-benzyl-5-(pyridin-2-yl-)pyrrolidine-2,4-dicarboxylate (173 mg, 0.490 mol, 98.0%, >95:5 dr) was obtained as a colorless solid: ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.48−8.45 (m, 1H) 7.57 (dt, J = 7.6, 2.0 Hz, 1H) 7.29−7.19 (m, 6H) 7.10 (ddd, J = 7.2, 4.8, 1.2 Hz, 1H) 4.48 (d, 6.8 Hz, 1H) 3.69 (s, 3H) 3.54 (bs, 1H) 3.22 (s, 3H) 3.17 (dt, J = 7.2, 4.8 Hz, 1H) 3.08 (d, J = 13.2 Hz, 1H) 2.93 (d, J = 13.2 Hz, 1H) 2.82 (dd, J = 13.6, 5.6 hz, 1H) 2.19 (dd, J = 13.6, 8.0 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 175.2, 172.8, 158.8, 148.8, 136.9, 136.1, 130.3, 127.9, 126.7, 122.3, 122.0, 70.5, 66.1, 52.1, 51.2, 49.5, 46.2, 38.3; IR (thin film) 3306, 3026, 2948, 1731, 1592, 1434, 1257, 1198, 745, 701 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{23}N_2O_4$ $[M + H]^+$ 355.1658, found 355.1651.

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Supporting Information Available: Experimental procedures and spectral data for all compounds generated through this work. This material is available free of charge via the Internet at http://pubs.acs.org.