Towards Organo-Click Chemistry: Development of Organocatalytic Multicomponent Reactions Through Combinations of Aldol, Wittig, Knoevenagel, Michael, Diels–Alder and Huisgen Cycloaddition Reactions

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Abstract: Here we report on our studies on combinations of amino acids and copper(I) for catalyzing multicomponent reactions (MCRs). We aimed to prepare both diene and dienophiles simultaneously, under very mild and environmentally friendly conditions, thus giving the constituents for a stereocontrolled Diels–Alder reaction, which in turn yields compounds **4** to **8**. A diversity-oriented synthesis of polysubstituted spirotriones **4** to **6** were assembled from simple substrates like 1-(triphenylphosphanylidene)-propan-2-one, two aldehydes, and cyclic-1,3-diketones through Wittig/Knoevenagel/Diels–Alder and aldol/Knoevenagel/Diels–Alder reaction sequences in one pot under stereospecific organocatalysis. Chemical diversity libraries of polysubstituted spirotrione-1,2,3-traizoles **8** were assembled from simple substrates by means of Wittig/Knoevenagel/Diels–Alder/Huisgen cycloaddition reaction sequences in one pot under stereospecific organo/Cu^{I} catalysis. Functionalized dispirolactones such as **6** are biologically active antioxidants and radical scavengers, and spirotrione-1,2,3-traizoles **8** have found wide applications in chemistry, biology, and materials science. Experimentally simple and environmentally friendly, organocatalytic, asymmetric four-component Diels–Alder (AFCDA) reactions of 1-(triphenylphosphanylidene)- propan-2-one, two different aldehydes, and cyclic-1,3-diketones produced diastereospecific and highly enantioselective substituted spirotriones **4** by means of a Wittig/Knoevenagel/Diels–Alder reaction sequence in one pot. Additionally we have developed an organocatalytic, asymmetric three-component Michael (ATCM) reaction of 1-(triphenylphosphanylidene)-propan-2-one, aldehyde, and cyclic-1,3-diketones that produced Michael adducts **15**, **16** through a Wittig/Michael reaction sequence in a highly enantioselective one-pot process.

Keywords: amino acids · cycloaddition · multicomponent reactions · organocatalysis · organo-click reactions

Introduction

Many organic reactions and reaction sequences have been developed for the construction of structurally complex polycyclic natural and non-natural products. More typically, these reactions and reaction sequences are not as efficient as enzymatic reactions in terms of selectivity (chemo-, regio-, diastereo-, and enantioselectivity) or in the ecology and economy of chemical reactions. From the synthetic chemist's point of view, ideal reaction strategies for preparation of structurally complex substances would involve sequences in which stereocontrolled formation of multiple carbon–carbon bonds occur in a single step starting from simple, readily available materials. As a result, great attention has been given to the development of multicomponent reactions (MCRs), because of their high degree of atom economy, their applications in combinatorial chemistry, and diversity-oriented synthesis.[1] Despite intense interest, there are few reports of diastereo- or enantioselective MCRs for the synthesis of stereochemically complex polycyclic compounds.[1d–f] A key to many interesting MCRs is the incorporation of a Diels–Alder and Huisgen cycloaddition reaction sequences to enable construction of complex polycycles in a completely stereocontrolled manner.[2]

Recent studies in our laboratory[3] have led to development of novel organocatalytic MCRs or asymmetric assembly reactions of simple substrates in one pot, such as organocatalytic asymmetric Michael/aldol,[3i] Knoevenagel/Michael,[3b] self-aldol,[3c] aldol/aldol,[3d] amination/aldol,[3e] Knoevenagel/Diels–Alder,[3f] and Knoevenagel/Diels–Alder/

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Experimental procedures, compound characterization, and analytical data (^{1}H NMR, ^{13}C NMR, and HRMS) for all new compounds (PDF). This material is available on the WWW under http://www.chemeurj.org/or from the author.

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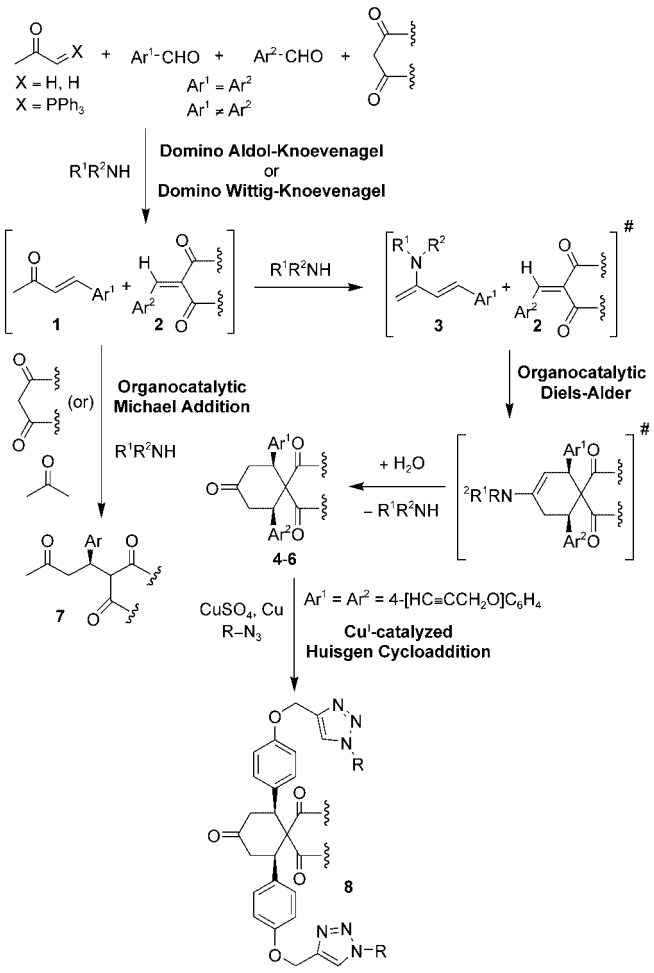
epimerization[3g,h] reaction sequences. These reaction conditions use less solvent and less toxic solvents than previously developed schemes and are thus significantly more environmentally friendly.[3a]

Here we describe the development of a set of powerful, reliable, and selective MCR's for the rapid synthesis of new compounds and combinatorial libraries through organo/Cu^{I}-catalyzed [4+2] and [3+2] cycloaddition reactions, an approach we call "organo-click chemistry". Recently K. B. Sharpless and co-workers have provided guidelines for click chemistry.[4] Ideally, organocatalytic MCR's fulfill all defining aspects of click chemistry, such as the reaction(s) must be modular, wide in scope, high yielding, generate only inoffensive byproducts, and be stereospecific.

In an extension of our work, we envisaged that asymmetric assembly of simple substrates like acetone or phosphorane, two different aldehydes, and 1,3-cyclic diketones under organoamine catalysis would provide complex polycyclic compounds thorugh aldol-condensation/Knoevenagel/Diels–Alder (A/K/DA), Wittig/Knoevenagel/Diels–Alder (W/K/DA), Wittig/Michael (W/M) and Knoevenagel/Michael (K/M) reaction sequences in one pot (Scheme 1). Further we envisaged that the stereospecific assembly of simple substrates like phosphorane, aldehydes, 1,3-cyclic diketones, and azides under organo/Cu^{I} catalysis would provide complex heterocyclic compounds by means of Wittig/Knoevenagel/Diels–Alder/Huisgen cycloaddition (W/K/DA/HC) reaction sequences in one pot (Scheme 1). We aimed to prepare both diene and dienophiles simultaneously, under very mild and environmentally friendly conditions, thus giving the constituents for a stereocontrolled Diels–Alder reaction, which in turn yields compounds **4** to **8** (Scheme 1). In this article, we describe the results of this investigation that provide for the organocatalytic stereospecific asymmetric assembly of polysubstituted 1,4-disubstituted 1,2,3-triazoles **8**, dispiro[5.2.5.2]hexadecanes **6**, spiro(cyclohexane-1,2′-indan)-triones **5**, spiro[5.5]undecanes **4**, and Michael adducts **15** and **16** from simple substrates in one pot. Dispirolactones **6** are bioactive molecules with antioxidant and radical scavenger activities[5c] and substituted 1,2,3-triazoles **8** have enabled a multitude of applications in biology, chemistry, and materials science.[5a,b,f] We have also developed a new method for the synthesis of both optical isomers of spirotriones **4** that involves a simple change in the order of addition of the reactants rather than a change in catalyst.



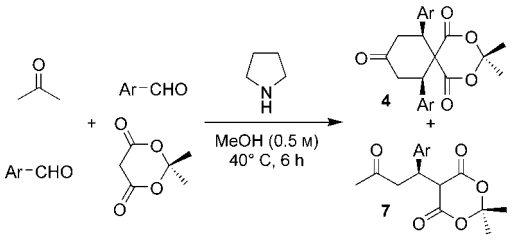
Scheme 1. Proposed organo/Cu^{I}-catalytic assembly of spirotriones and spirotrione–triazoles via simultaneously organogenerated diene and dienophiles in aldol (or Wittig)/Knoevenagel/Diels–Alder and Wittig/Knoevenagel/Diels–Alder/Huisgen cycloaddition reaction sequences in one pot.

In our reaction we envisioned that amino acids and amines would catalyze the domino aldol condensation of an aldehyde with acetone (or with phosphorane in an uncatalyzed Wittig reaction) to provide *trans*-enone **1** (diene source). Knoevenagel condensation of an aldehyde with 1,3-cyclic diketones would provide arylidene–cyclic diketones (**2**; dienophile), which would then undergo a concerted [4+2] cycloaddition with a 2-amino-1,3-butadiene (**3**) generated in situ from *trans*-enone **1** and amino acid or amine to form substituted spirotriones **4** to **6** in a diastereoselective manner (Scheme 1). Propargyl substituted spirotriones **4** to **6** would undergo regiospecific [3+2] cycloaddition with azides to generate 1,2,3-triazoles **8** under $CuSO_4$/Cu catalysis in one pot. Enones **1** and **2** could also be directed to undergo asymmetric Michael additions with 1,3-cyclic diketones or acetone under amino acid or amine catalysis to furnish compounds **7**. The domino A/K/DA or W/K/DA and W/K/DA/HC reaction would then generate a quaternary center with formation of four new carbon–carbon σ bonds and four new carbon–nitrogen σ bonds, respectively.

Results and Discussion

Domino aldol/Knoevenagel/Diels–Alder reactions: We were pleased to find that the three-component reaction of acetone, benzaldehyde, and Meldrum's acid with a catalytic amount of pyrrolidine in methanol at 40 °C for 6 h furnished the Diels–Alder product **4a** as single diastereomer in 65% yield accompanied by the Michael adduct **7a** in 20% yield (Table 1, entry 1). The three-component A/K/DA reaction of benzaldehyde containing an electron-withdrawing group (4-NO_2) furnished spirotrione **4b** as single diastereomer in 66% yield and the Michael adduct **7b** in 15% yield (Table 1, entry 2). Unfortunately, the hetero-domino A/K/DA reaction of acetone, 4-$NO_2C_6H_4CHO$, and Meldrum's

Table 1. Diastereospecific and chemoselective three-component Aldol/Knoevenagel/Diels–Alder reaction sequence catalyzed by pyrrolidine in one pot.[a]



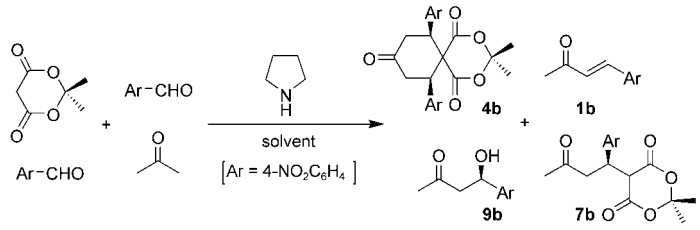
Entry	Ar	Products	Yield [%][b]		d.r.[c]
			4	**7**	
1	C_6H_5	**4a**,**7a**	65	20	>100:1
2[d]	4-$NO_2C_6H_4$	**4b**,**7b**	66	15	>100:1
3[e]	4-$NO_2C_6H_4$	**4b**,**7b**	51	5	>100:1
4	4-$MeOC_6H_4$	**4c**,**7c**	72	20	>100:1
5[f]	4-$MeOC_6H_4$	**4c**,**7c**	57	43	>100:1

[a] Experimental conditions: pyrrolidine (0.15 mmol), aldehyde (1.0 mmol), Meldrum's acid (0.5 mmol), and acetone (1 mmol) in methanol (0.5 mL) were stirred at 40 °C for 6 h (see Experimental Section). [b] Yield refers to the purified product obtained by column chromatography. [c] Ratio based on ^{1}H NMR analysis of unpurified products. [d] Reaction time 20 h. [e] Reaction was performed at 25 °C for 72 h. [f] In this reaction acetone was used as solvent.

acid under L-proline catalysis furnished the spirotrione **4b** in very low yields. The pyrrolidine-catalyzed three-component A/K/DA reaction of acetone, 4-nitrobenzaldehyde, and Meldrum's acid revealed that yields of this reaction varied with solvent as shown in Table 2. The highly electrophilic nature of 4-nitrobenzaldehyde furnished the byproduct alcohol **9b** under pyrrolidine catalysis in the domino A/K/DA reaction, but did not generate the alcohols **9** with other aldehydes (Tables 1 and 2). Pyrrolidine-catalyzed A/K/DA reaction of benzaldehyde with an electron-donating group (4-MeO) furnished the spirotrione **4c** in 72% yield and the Michael adduct **7c** in 20% yield (Table 1, entry 4). Based on these results, our organocatalytic three-component A/K/DA reaction should find utility in the generation of libraries of spirotriones **4** with good to moderate yields in a diastereospecific manner from simple substrates.

Reaction mechanism: The proposed mechanism of diastereospecific assembly of *cis*-spiranes (**4**) and Michael adducts (**7**) in the MCRs of acetone, aldehyde, and Meldrum's acid under pyrrolidine catalysis is illustrated in Scheme 2. First, reaction of pyrrolidine with aldehyde generates the imine cation **10**, an excellent electrophile that undergoes Mannich type reactions with enolates or enamines of acetone and Meldrum's acid to generate Mannich products **11** and **12**, respectively. Retro-Mannich or base-induced elimination reaction of amino–ketones **11** and **12** under basic conditions would furnish *trans*-enone **1** and benzylidene–Meldrum's acid **2**, respectively. Compound **2** is a reactive dienophile that undergoes a Diels–Alder or a double Michael reaction with the soft nucleophile 2-amino-1,3-butadiene **3**, generated in situ from *trans*-enone **1** and an amine catalyst, to produce the A/K/DA product **4**. Compound **2** can also react with enolate (or enamine) of acetone to produce domino K/M product **7**. The ratio of domino products **4** and **7** is dependent on the electrophilicity of imine **10**, dienophile **2**, reaction temperature, and concentration of acetone in the reaction media (Table 1, entries 3, 4, and 5). Formation of *trans*-enones **1** (diene source) and dienophiles **2** by means of Mannich and retro-Mannich reactions support our hypothesis that aldol products **9** did not form in these reactions, with the exception of reaction with the highly reactive 4-$NO_2C_6H_4$-CHO. This hypothesis is also supported by the mechanistic investigation of pyrrolidine-catalyzed enal formation through aldehyde self-condensation reported by Saito et al.[6]

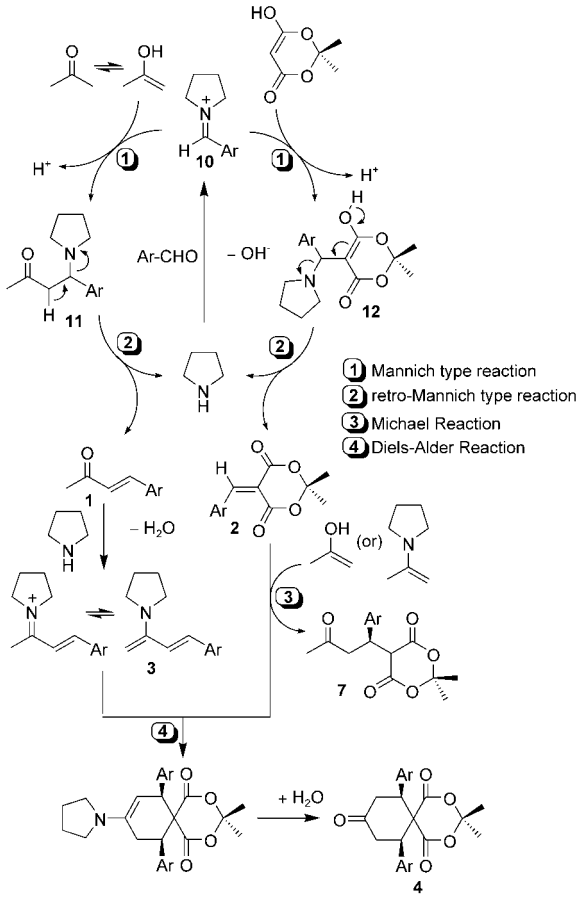
Table 2. Effect of solvent on the direct pyrrolidine-catalyzed stereospecific three-component aldol/Knoevenagel/Diels–Alder reaction of 4-nitrobenzaldehyde, Meldrum's acid, and acetone in one pot.[a]



Entry	Solvent [0.5 M]	*T* [°C]	*t* [h]	Products	Yield[b] [%]	Ratio[c] [**4b**:**1b**:**9b**]
1[d]	MeOH	25 °C	72	**4b**,**1b**,**7b**	63	5.3:1:0
2[d],[e]	MeOH	25 °C	72	**4b**,**1b**,**9b**,**7b**	65	5.3:1:1
3[f]	MeOH	25 °C→40 °C	22	**4b**,**1b**,**9b**,**7b**	80	6:1:1
4[f]	EtOH	25 °C	72	**4b**,**1b**,**9b**,**7b**	70	4:3:1
5[f]	DMF	25 °C	72	**4b**,**1b**,**7b**	63	5:1:0
6[f]	THF	25 °C	72	**4b**,**1b**,**9b**,**7b**	65	3.5:5:1
7[f]	CH_3CN	25 °C	72	**4b**,**1b**,**9b**,**7b**	65	7:3:1
8[f]	$CH_3C_6H_5$	25 °C	72	**4b**,**1b**,**9b**,**7b**	75	1:2.5:1
9	[bmim]BF_4	40 °C	17	**4b**,**9b**	50	30:0:1
10	H_2O	25 °C→40 °C	72	**4b**,**1b**,**9b**	30	2:1:3.5

[a] Experimental conditions: pyrrolidine (0.15 mmol), 4-nitrobenzaldehyde (1.0 mmol), and Meldrum's acid (0.5 mmol) in solvent (0.5 mL) were stirred at ambient temperature for 20 minutes then acetone (1 mmol) was added (see Experimental Section). [b] Yield refers to the purified product obtained by column chromatography. [c] Ratio based on ^{1}H NMR analysis of unpurified products. [d] 5% of domino Knoevenagel/Michael product **7b** was isolated. [e] Acetone was taken in excess (2 mmol). [f] 10–15% of domino Knoevenagel/Michael product **7b** was isolated.

Domino Wittig/Knoevenagel/Diels–Alder reactions: To avoid the formation of byproducts in the domino A/K/DA reactions, we developed a new reaction sequence for the stereospecific assembly of spirotriones by means of three-component W/K/DA reaction in one-pot under organocatalysis. We found that the three-component reaction of 1-(triphenylphosphanylidene)-propan-2-one, benzaldehyde, and Meldrum's

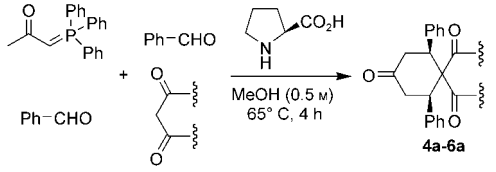


Scheme 2. Proposed catalytic cycle for the simultaneous organogeneration of diene and dienophiles in pyrrolidine-catalyzed aldol/Knoevenagel/Diels–Alder and Knoevenagel/Michael reaction sequences in one pot.

acid with a catalytic amount of L-proline in methanol at 65 °C for 4 h furnished Diels–Alder product **4a** as a single diastereomer in 80 % yield (Table 3, entry 1). Under the same reaction conditions, different 1,3-cyclic diketones furnished the expected spirotriones **5a** and **6a** in very good yields as shown in Table 3. Medicinally important dispirolactone **6a** was furnished in 99 % yield under optimized conditions (Table 3, entry 4). Chemical diversity libraries of spiranes **4**, **5**, and **6** could therefore be prepared easily by using the W/K/DA reaction sequence in a single reaction vessel.

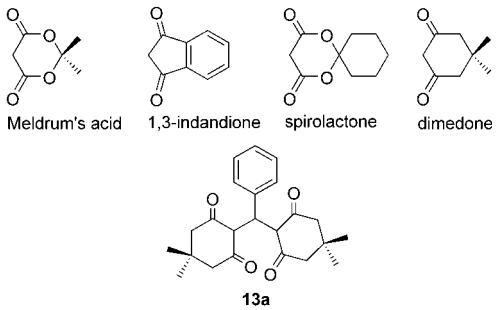
Interestingly, the three-component reaction of 1-(triphenylphosphanylidene)-propan-2-one, benzaldehyde, and dimedone with a catalytic amount of L-proline in methanol at 65 °C for 2 h furnished the unexpected product **13a** in 85 % yield (Table 3, entry 5) without the expected Diels–Alder product **14a**. The same reaction at room temperature also furnished **13a** in very good yield (Table 3, entry 6). Formation of **13a** in the W/K/DA reaction can be explained due to more favorable soft–soft interactions of the dienophile (5,5-dimethyl-2-benzylidene-cyclohexane-1,3-dione) and dimedone (pK_a 11.2, in DMSO at 25 °C)[7e] as compared to Meldrum's acid (pK_a 7.3, in DMSO at 25 °C).[7e] The soft acidic nature of dimedone was further established in three-component Knoevenagel/Diels-Alder (K/DA) reaction as shown in Scheme 3, in which the less reactive dienophile (5,5-dimethyl-2-(4-nitro-benzylidene)-cyclohexane-1,3-dione) was generated. Organocatalytic K/DA reaction of enone **1a**, 4-nitrobenzaldehyde, and dimedone under L-proline catalysis at room temperature also furnished the **13b** in 81 % yield without **14b**. Organo-generated aldehyde–dimedone adducts, which are called dimethones, are very useful materials in medicinal chemistry (anticonvulsant, antidepressant, diuretic, antibacterial, antitumor, or anticarcinogenic activity).[7b–d] Amino acid catalyzed dimethone formation may also find application in the analysis of aldehydes in foods.[7a]

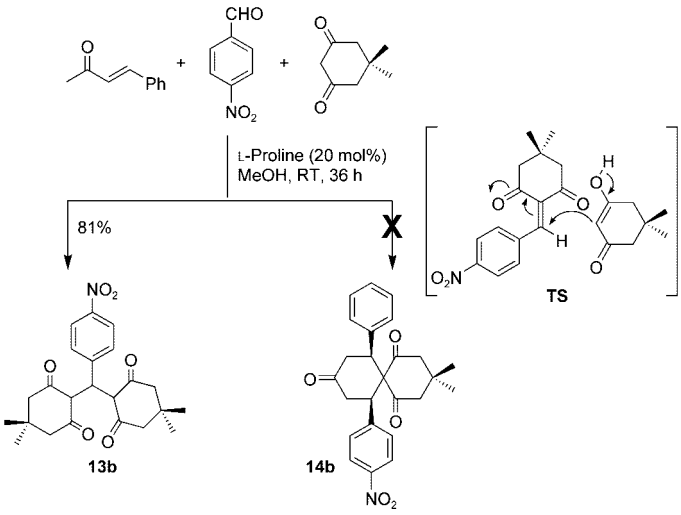
Table 3. Stereospecific assembly of spirotriones through the three-component Wittig/Knoevenagel/Diels–Alder reaction sequence in one pot under L-proline catalysis.



Entry	1,3-Cyclic diketone	Product	Yield[%]	d.r.
1	Meldrum's acid	**4a**	80	>100:1
2	1,3-indandione	**5a**	84	23:1
3	spirolactone	**6a**	91	>100:1
4[a]	**spirolactone**	**6a**	**99**	**>100:1**
5[b]	dimedone	**13a**	85	–
6[c]	dimedone	**13a**	95	–

[a] Ethanol was used as solvent. [b] Reaction time was 2 h. [c] Reaction performed at 25 °C for 5 h.



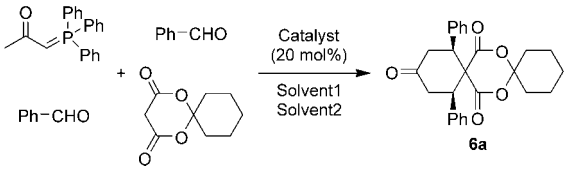


Scheme 3. Formation of unexpected product **13b** in organocatalytic Knoevenagel/Diels–Alder reaction.

Effects of solvent, temperature, and amine on the direct amine-catalyzed stereospecific three-component W/K/DA reaction of phosphorane, benzaldehyde, and spirolactone in one pot are shown in Table 4. Domino W/K/DA product **6a** was formed in very good yields under L-proline catalysis, but dispirolactone **6a** was formed in moderate yields under

Effect of amine and solvent on the Wittig reaction: Neither the type of amino acid or amine catalyst nor the use of protic solvents (MeOH, EtOH) had an effect on the stereochemistry of the Wittig reaction of aldehydes with phosphorane; these reactions furnished only the *trans*-enones (**1**) as shown in Scheme 4.[9]

Table 4. Effect of solvent and amine on the direct amine-catalyzed stereospecific three-component Wittig/Knoevenagel/Diels–Alder reaction of phosphorane, benzaldehyde, and spirolactone in one pot.

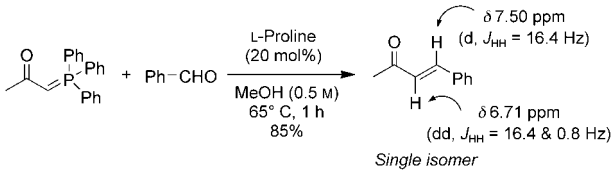


Entry	Catalyst	Solvent1	Solvent2	T [°C]	t [h]	Yield [%][c]	d.r.[d]
1[a]	L-proline	C_6H_6	MeOH	65→25	1→48	86	>100:1
2[a]	L-proline	C_6H_6	MeOH	65→65	0.5→12	99	>100:1
3[b]	L-proline	MeOH	MeOH	25	48	90	>100:1
4[b]	L-proline	MeOH	MeOH	65	4	91	>100:1
5[b]	pyrrolidine	MeOH	MeOH	25	72	62	>100:1
6[b]	pyrrolidine	MeOH	MeOH	65	2	67	>100:1
7[b]	**L-proline**	**EtOH**	**EtOH**	**65**	**4**	**99**	**>100:1**

[a] Experimental conditions: benzaldehyde (0.75 mmol) and 1-(triphenylphosphanylidene)-propan-2-one (0.25 mmol) in benzene (0.1 mL) were stirred at 65 °C for 0.5 to 1 h then proline (0.05 mmol), 1,3-cyclic diketone (0.25 mmol), and methanol (0.5 mL) was added and stirred (see Experimental Section). [b] All reactants mixed at once with same proportions as above in solvent (0.5 mL) and stirred (see Experimental Section). [c] Yield refers to the purified product obtained by column chromatography. [d] Ratio based on ^{1}H NMR analysis of purified products.

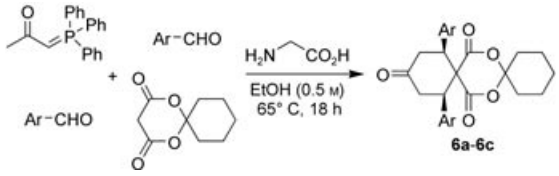
Chemical diversity libraries of potential antioxidants: We further explored the potential of the L-proline-catalyzed heterodomino W/K/DA reaction for the synthesis of diverse libraries of antioxidant dispirolactones (**6**) with various arylaldehydes. Upon simple heating of phosphorane, aldehydes, and spirolactone with a catalytic amount of proline, almost quantitative conversion to the dispiro-[5.2.5.2]hexadecanes **6** was observed. The excellent results in Table 6 establish the scope of this reaction, which readily accepts complex carbohydrate synthons (see **6r**). This procedure is a manifestation of an

amine (pyrrolidine) catalysis as shown in Table 4. Interestingly, the primary amino acid glycine also catalyzed the three-component W/K/DA reaction of phosphorane, aldehydes, and spirolactone under physiological conditions to generate stereospecific spirotriones **6** in one pot as shown in Table 5. Yields of spirotriones **6** obtained under glycine cat-



Scheme 4. Effect of L-proline and methanol on the stereochemistry of the Wittig reaction.

Table 5. Glycine-catalyzed stereospecific assembly of spirotriones via three-component Wittig/Knoevenagel/Diels-Alder reaction sequence in one pot.[a]



Entry	Ar	Products	Yield [%]	d.r.
1	C_6H_5	**6a**	62	>100:1
2	4-$NO_2C_6H_4$	**6b**	55	>100:1
3	4-$MeOC_6H_4$	**6c**	73	>100:1
4[b]	C_6H_5	**6a**	31	>100:1
5[c]	4-$MeOC_6H_4$	**6c**	<5	>100:1

[a] See Experimental Section. [b] Water (1 mL) was used as solvent. [c] Reaction performed at 25 °C for 5 days, enone **1c** and Knoevenagel products were isolated in 90 and 86 % yield, respectively.

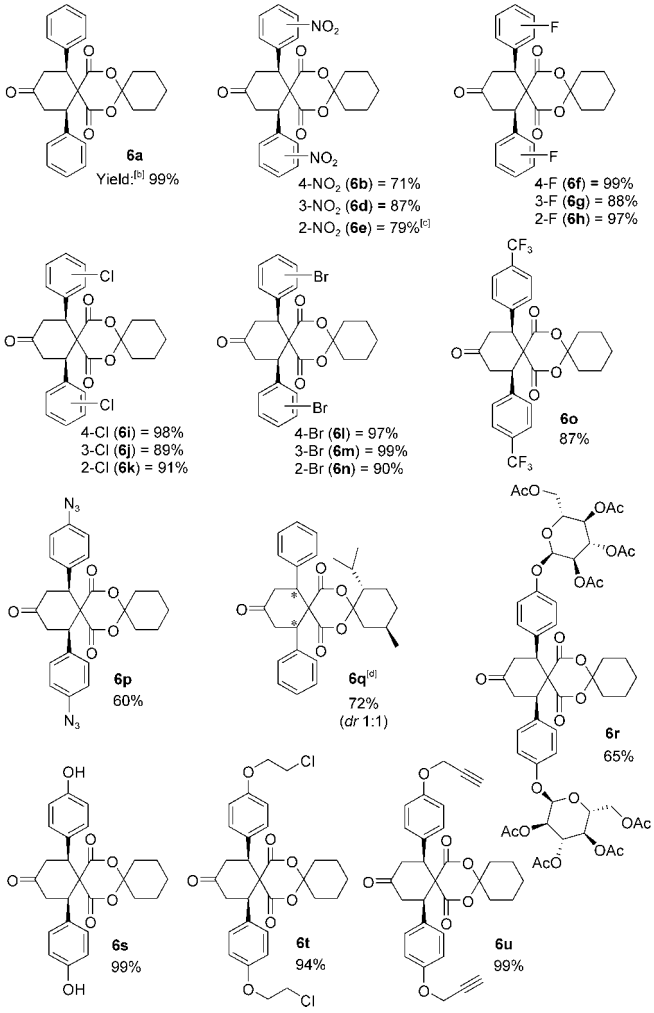
alysis were, however, typically less than those obtained under proline catalysis. Glycine catalyzed reactions are significant in understanding the reaction-potential of the prebiotic world.[8]

"organo-click chemistry" transformation. Each of the targeted prochiral dispirolactones **6** was obtained as a single diastereomer. As the reaction proceeds, the mixture solidifies as the product is formed.

Antioxidant dispirolactones (**6**) were generated in good yields with aromatics bearing hydroxy, propargyl, azide, and glucose moieties in the *para*-position as shown in Table 6. Dispirolactone **6r** is an analogue of the antioxidative glucoside isolated from oregano (*Origanum vulgare*).[10] Prochiral *cis*-spiranes **6a–e**, **j**, **k**, **m** are anti-oxidants/free-radical scavengers. Generation of molecular diversity around this scaffold may allow for the identification of more potent species. The method described here for the synthesis of these antioxidants offers significant improvements in synthetic ease and yields as compared to previous routes.[5c]

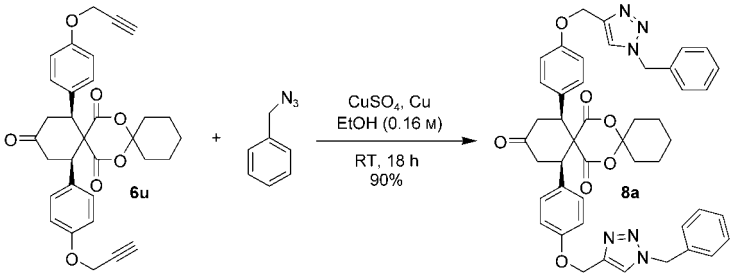
Wittig/Knoevenagel/Diels-Alder/Huisgen cycloaddition reactions in one pot: Huisgen 1,3-dipolar cycloaddition reactions[2a–c,g] are exergonic fusion processes, and the cycloaddition of azides and alkynes to give triazoles is arguably the

Table 6. Stereospecific synthesis of chemically diverse libraries of antioxidant polysubstituted dispiro[5.2.5.2]hexadecanes by means of Wittig/Knoevenagel/Diels–Alder reaction sequence in one pot.[a]



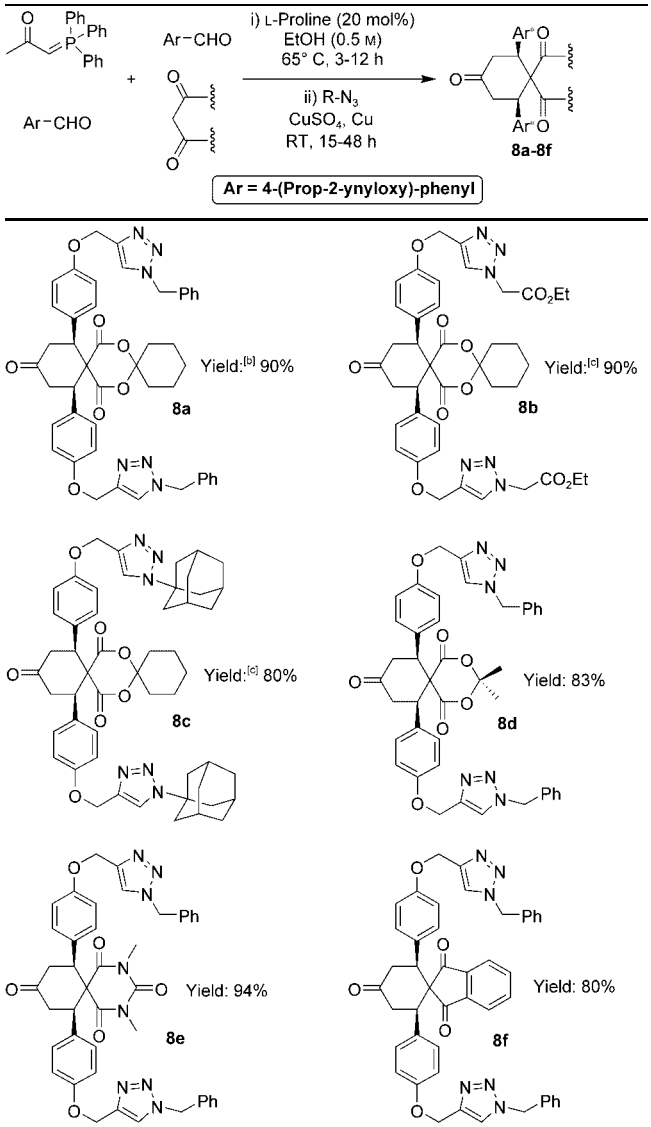
[a] All reactions were carried out in EtOH (0.5 M), with 20 mol% of L-proline at 65 °C, and complete in 3–12 h. [b] Yield refers to the column purified product. [c] Reaction time was 20 h. [d] Product obtained from K/DA reaction.

most useful members of this family. Huisgen cycloaddition of propargyl-substituted dispiro[5.2.5.2]hexadecane **6u** with benzyl azide under $CuSO_4$/Cu catalysis furnished the regiospecifically 1,4-disubstituted 1,2,3-triazole **8a** in very good yield as shown in Scheme 5. 1,2,3-Triazoles have found wide applications in biology, chemistry, and materials science.[5a,b,f] Therefore, it is important to develop new and more efficient MCR approaches to diverse arrays of 1,2,3-triazoles in one-pot. We were pleased to find that the in situ generated dispiro[5.2.5.2]hexadecane **6u** under proline catalysis further reacted with benzyl azide in same solvent under $CuSO_4$/Cu-catalysis to furnish the expected spirotrione-1,2,3-triazole (**8a**) in 90% yield with formation of four new carbon–carbon σ bonds and four new carbon–nitrogen σ bonds in one pot. The scope of this proline/Cu^I-catalyzed spirotrione–triazole synthesis is partly revealed by the examples in Table 7. Variously substituted azides and 1,3-cyclic diketones readily participate in this one-pot transformation.



Scheme 5. Regiospecific synthesis of 1,4-disubstituted 1,2,3-triazole **8a** catalyzed by Cu^I ions in the presence of Cu wire.

Table 7. Organo/Cu^I-catalyzed stereospecific synthesis of polysubstituted triazoles through Wittig/Knoevenagel/Diels–Alder/Huisgen cycloaddition reactions in one pot.[a]

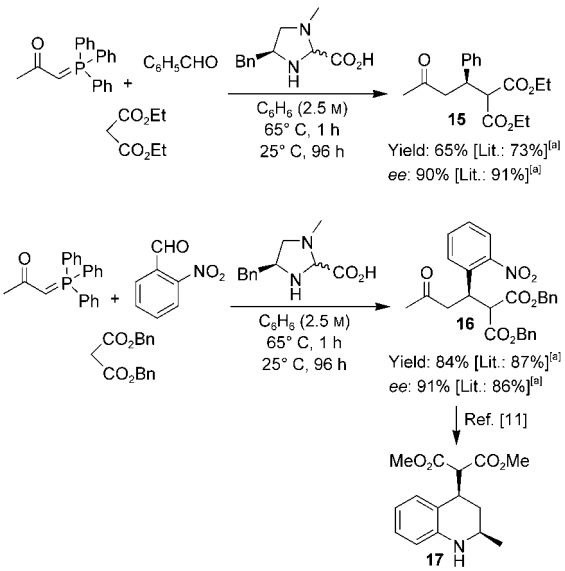


[a] See Experimental Section. [b] Yield refers to the column purified product. [c] Huisgen cycloaddition was slow at 25 °C (48 h), but at 50 °C reaction completed within 5-10 h.

Asymmetric four-component Diels–Alder (AFCDA) reactions: Recently we developed the L-DMTC-catalyzed (L-5,5-dimethyl thiazolidinium-4-carboxylate) asymmetric three-

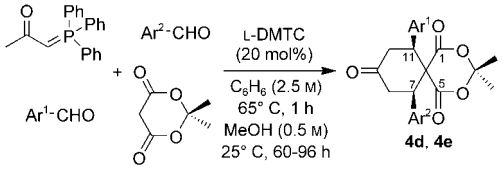
component Diels–Alder (ATCDA) reaction of *trans*-enone, aldehyde, and Meldrum's acid to produce substituted spiro[5.5]undecanes in very good yields and useful enantiomeric excess (*ee*). These compounds are useful starting materials for the synthesis of exotic amino acids.[3f] The versatility of the ATCDA reaction was improved by optimization as an asymmetric four-component Diels–Alder (AFCDA) reaction with a L-DMTC-catalyzed W/K/DA reaction sequence in one pot (Table 8). Reaction of phosphorane, benzaldehyde, 4-nitrobenzaldehyde, Meldrum's acid, and L-DMTC in methanol furnished a single diastereomer, spirane (7*R*,11*S*)-**4d** in 83% yield and 69% *ee* (Table 8, entry 1).

Significantly, the antipode of the optical isomer can obtained by simply changing the addition sequence of starting materials in reaction mixture without changing the catalyst as shown in Table 8. This technique provides for the synthesis of both optical isomers of a number of spiranes (**4**) in good yields and *ee*'s. For example, the optical antipode of (7*R*,11*S*)-**4d** was obtained in 80% yield and 42% *ee* by changing the addition sequence of C_6H_5CHO and 4-$NO_2C_6H_4CHO$. The enantiomeric excess of (7*S*,11*R*)-**4d** was increased to 90% by recrystalising in 15% isopropanol/hexane (the mother liquor is enantioenriched). Two additional examples are shown in Table 8.



Scheme 6. Organocatalytic asymmetric three-component Michael (ATCM) reactions. [a] Literature values from two-component reactions obtained byK. A. Jorgensen et al.[11]

Table 8. Organocatalytic asymmetric four-component Wittig/Knoevenagel/Diels–Alder reaction sequence used to generate diastereospecific and enantioselective synthesis of spirolactones in one pot.[a]



Entry	Ar^1	Ar^2	Yield[%]	d.r.	*ee*[b]	Absolute[c] configuration
1[d]	C_6H_5	4-$NO_2C_6H_4$	83	>100:1	69	(7*R*,11*S*)-**4d**
2[d]	4-$NO_2C_6H_4$	C_6H_5	80	>100:1	42	(7*S*,11*R*)-**4d**
3[e]	C_6H_5	4-CNC_6H_4	85	>100:1	70	(7*R*,11*S*)-**4e**
4[e]	4-CNC_6H_4	C_6H_5	80	>100:1	42	(7*S*,11*R*)-**4e**

[a] Experimental conditions: aldehyde, Ar1-CHO (0.5 mmol), and 1-(triphenylphosphanylidene)-propan-2-one (0.5 mmol) in benzene (0.2 mL) were stirred at 65°C for 1 h, then L-DMTC (0.1 mmol), aldehyde, Ar2-CHO (0.5 mmol), Meldrum's acid (0.5 mmol), and methanol (1.0 mL) were added and stirred at 25°C (see Experimental Section). [b] Enantiomeric excesses were determined using chiral-phase HPLC. [c] Absolute configuration determined based on HPLC analysis and comparison to earlier reports. [d] Spirotriones **4a** and **4b** are formed in 2:1 ratio with 10% yield. [e] Spirotrione **4f** is formed in 10% yield.

Asymmetric three-component Michael (ATCM) reactions: *trans*-Enones **1** prepared in situ by means of the Wittig reaction were also studied in the asymmetric Michael reaction of 1,3-cyclic diketones under organocatalysis as recently reported by Jorgensen et al.[11] As shown in Scheme 6, the novel asymmetric three-component Michael (ATCM) reaction of phosphorane, benzaldehyde, and diethyl malonate under imidazolidine catalysis furnished the Michael adduct **15** in 65% yield and 90% *ee*. The ATCM reaction of phosphorane, 2-$NO_2C_6H_4CHO$, and dibenzyl malonate furnished the expected product **16** in 84% yield and 91% *ee*, comparable to the previously disclosed two-component reaction yields. The rate of the Michael reaction in ATCM was fast relative to the two-component reaction presumably due to the basic nature of byproduct triphenylphosphoxide.

Conclusion

In conclusion, we have demonstrated for the first time the organo/Cu^I-catalyzed enzyme-like assembly of spirotriones **4**, **5**, **6**, and **8** from readily available precursors by means of A/K/DA, W/K/DA, and W/K/DA/HC reaction sequences. Combination of proline/Cu^I-ions proved to be compatible organo/metal catalysts for the MCRs in one pot. This simple one-pot procedure provides direct access to functionalized dispirolactones (**6**), shown to be antioxidants and radical scavengers in biological studies. Glycine was also a functional organo catalyst in some systems. Multicomponent reactions catalyzed by glycine may be significant in understanding the potential chemistries available to the prebiotic world. Significantly, we developed an AFCDA reaction scheme that yields both optical isomers of **4** simply by changing the order of reactant addition. Additionally, a novel organocatalytic ATCM reaction was developed. These reactions can be performed on a multigram scale under operationally simple and environmentally safe conditions. These results suggest that the assembly of complex products from simple starting materials is within the realm of organocatalysis involving simple amino acids and amines. Further

studies aimed at exploring the scope of assembly reactions of these types are ongoing.

Experimental

General methods: The ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$ ppm) for ^{1}H NMR spectra and relative to the central $CDCl_3$ resonance ($\delta = 77.0$ ppm) for ^{13}C NMR spectra. Coupling constants in ^{1}H NMR measurements are given in Hz. In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT-135 experiment, and is given in parentheses. Flash chromatography (FC) was performed by using silica gel Merck 60 (particle size 0.040–0.063 mm). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix. Electrospray ionization (ESI) mass spectrometry was performed on an API 100 Perkin–Elmer SCIEX single quadrupole mass spectrometer. The enantiomeric excess (*ee*) of the products were determined by HPLC using Daciel chiralcel OD-H or Daciel chiralpak AS or Daciel chiralpak AD columns with *i*-PrOH/hexane as eluent. HPLC was carried out by using a Hitachi organizer consisting of a D-2500 Chromato-Integrator, an L-4000 UV-Detector, and an L-6200A Intelligent Pump. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

Materials: All solvents and commercially available chemicals were used as received. 1,5-Dioxaspiro[5.5]undecane-2,4-dione and 7-isopropyl-10-methyl-1,5-dioxaspiro[5.5]undecane-2,4-diones are prepared cyclizing corresponding cyclohexanone and (−)-menthone with malonic acid in acetic anhydride under catalysis of concentrated H_2SO_4 or *p*-TSA at 20 to 50 °C for 5–10 h, aqueous work-up and recrystallization with petroleum ether furnished spiro[5.5]undecane-2,4-diones. Catalyst 4-benzyl-1-methyl-imidazolidine-2-carboxylic acid (d.r. = 2:1),[12] 4-$N_3C_6H_4CHO$,[13] and 4-[(2,3,4,6-tetra-O-acetyl-D-glucopyranosyl)oxy]benzaldehyde[14] are prepared according to literature procedures.

General experimental procedures for organo-click reactions

Pyrrolidine-catalyzed domino A/K/DA and K/M reactions: In an ordinary glass vial equipped with a magnetic stirring bar, solvent (0.5 mL) was added to the aldehyde (1.0 mmol), Meldrum's acid (0.5 mmol) and acetone (1.0 mmol), followed by the addition of the catalyst pyrrolidine (0.15 mmol). The reaction mixture was stirred at 40 °C for the time indicated in Tables 1 and 2. The crude reaction mixture was directly loaded on silica gel column without aqueous workup and pure domino K/A/DA and K/M products **4a–c** and **7a–c** were obtained by flash column chromatography (silica gel, mixture of hexane/ethyl acetate).

Amino acid and amine-catalyzed domino W/K/DA reactions: For the synthesis of antioxidants **6**, reactants 1-(triphenylphosphanylidene)-propan-2-one (0.5 mmol), aldehyde (1.3 mmol), 1,5-dioxa-spiro[5.5]undecane-2,4-dione (0.5 mmol), and L-proline, glycine or pyrrolidine (0.1 mmol) in ethanol (1.0 mL) were placed in an ordinary glass vial equipped with a magnetic stirring bar and stirred at 65 °C for the time indicated in Tables 3–6. The crude reaction mixture was directly loaded on silica gel column without aqueous workup, and pure domino antioxidant products **6a–u** were obtained by flash column chromatography (silica gel, mixture of hexane/ethyl acetate).

L-Proline/Cu^I-catalyzed W/K/DA/HC reactions in one pot: For the synthesis of spirotrione-triazoles **8**, reactants 1-(triphenylphosphanylidene)-propan-2-one (0.25 mmol), 4-prop-2-ynyloxy-benzaldehyde (0.6 mmol), 1,3-cyclic diketone (0.25 mmol) and L-proline (0.05 mmol) in ethanol (0.5 mL) were placed in an ordinary glass vial equipped with a magnetic stirring bar and stirred at 65 °C for the time indicated in Table 7. $CuSO_4$ (0.25 mmol), Cu wire (3 mg), and azide (1.2 mmol) were added to the crude reaction mixture and stirred at room temperature for the time indicated in Table 7. The crude reaction mixture was directly loaded on silica gel column without aqueous workup and pure spirotrione–triazole products **8a–f** were obtained by flash column chromatography (silica gel, mixture of hexane/ethyl acetate).

L-DMTC-catalyzed AFCDA reactions in one pot: A solution of Aldehyde, Ar^1-CHO (0.5 mmol) and 1-(triphenylphosphanylidene)-propan-2-one (0.5 mmol) in benzene (0.2 mL) was stirred at 65 °C for 1 h; then L-DMTC (0.1 mmol), aldehyde, Ar^2-CHO (0.5 mmol), Meldrum's acid (0.5 mmol), and methanol (1.0 mL) were added and stirred at 25 °C for the time indicated in Table 8. The crude reaction mixture was treated with saturated aqueous ammonium chloride solution, the layers were separated, and the organic layer was extracted three to four times with dichloromethane, dried with anhydrous Na_2SO_4, and evaporated. The pure AFCDA products **4d** and **4e** were obtained by flash column chromatography (silica gel, mixture of hexane/ethyl acetate). Enantiomeric excesses (*ee*) and NMR spectra of pure AFCDA products were compared with our previous report of ATCDA products.[3f]

Imidazolidine-catalyzed ATCM reactions in one pot: A solution of aldehyde (0.5 mmol) and 1-(triphenylphosphanylidene)-propan-2-one (0.5 mmol) in benzene (0.2 mL) was stirred at 65 °C for 1 h; then 4-benzyl-1-methyl-imidazolidine-2-carboxylic acid (0.05 mmol) and diethyl malonate or dibenzyl malonate (0.5 mL) were added and stirred at 25 °C for the time indicated in Scheme 6. The pure ATCM products **15** and **16** were obtained by flash chromatography directly from crude reaction mixture; NMR spectra and *ee*'s of the ATCM products were compared with literature values, which were obtained from two-component reactions.[11]

Acknowledegments

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