Multicomponent Reactions

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Stereoselective Palladium-Catalyzed Four-Component Cascade Synthesis of Pyrrolidinyl-, Pyrazolidinyl-, and Isoxazolidinyl Isoquinolines**

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One-pot multicomponent reactions (MCRs) provide a rapid and elegant means for the preparation of complex molecular architectures from readily available building blocks.[1–5] Among the advantages of MCRs are yields that are higher than almost any sequential synthesis of the same target, a single purification step, and easy adaptation to combinatorial synthesis.

In recent years, allenes have become useful building blocks in palladium catalyzed processes.[6,7] We have demonstrated that carbon monoxide and allenes are powerful relay switches in palladium-catalyzed cyclization–anion-capture

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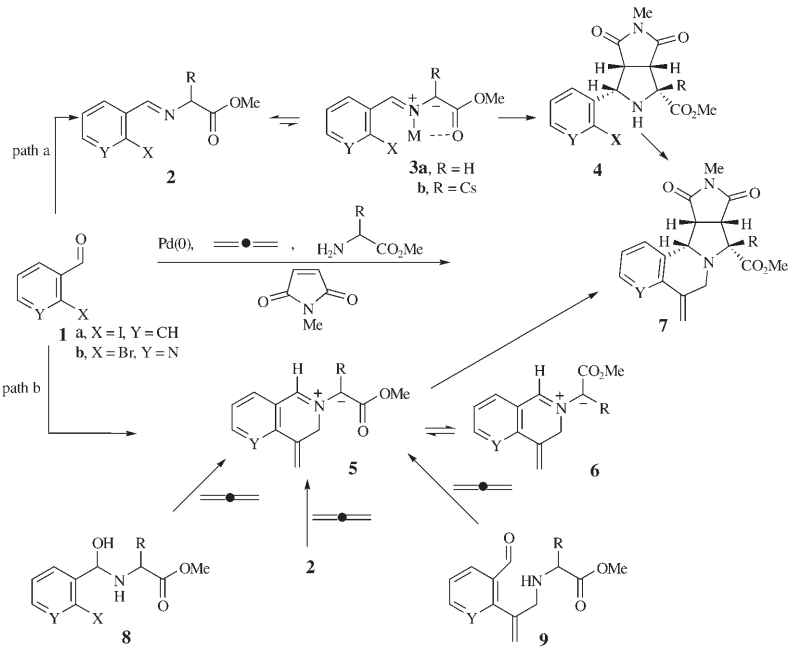
Supporting information for this article, including general experimental procedures and selected examples, is available on the WWW under http://www.angewandte.org or from the author.

cascades.[1,6,7] As part of our ongoing interest in the design of palladium-catalyzed allenylation processes in a tactical combination with core reactions, we have explored combinations that have 1,3-dipolar cycloaddition processes as the key step in the synthesis of heterocycles.[8] Herein we report four-component cascades with 2-iodoaryl aldehyde **1a** or 2-bromoaryl aldehyde **2b** (Scheme 1) that generate azomethine ylides, azomethine imines, and nitrones as integral parts of the cascade.

Aldehydes **1a** and **b** react, through path a or path b, with an allene, an α-amino acid methyl ester, and *N*-methyl maleimide (NMM) in the presence of Pd^0 to afford **7** (Scheme 1). Path a involves the formation of imine **2**, which undergoes 1,3-dipolar cycloaddition via azomethine ylide **3a** or **3b** (*endo* transition state) to give **4**.[9] Successive palladium-catalyzed allene/nucleophile incorporations then afford **7**. Path b proceeds by initial palladium-catalyzed allene/nucleophile incorporation to generate azomethine ylide **5**, which then undergoes 1,3-dipolar cycloaddition to afford **7**. Azomethine ylide **5** could arise through the precursors **2**, **8**, or **9**.

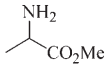
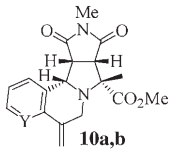
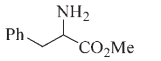
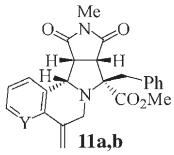
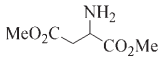
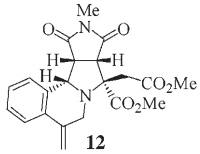
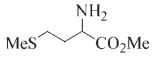
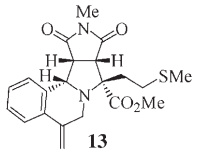
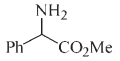
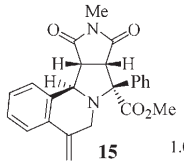
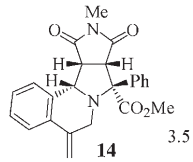
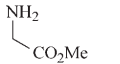
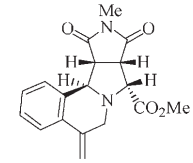
Our hope was that, if successful, the configuration of the product could be used to distinguish between paths a and b (Scheme 1) as the cycloaddition of *N*-alkylated azomethine ylides **5**/**6** has a different stereochemical outcome to those of **3a**/**3b**.[9]

2-Iodoaldehyde **1a** or 2-bromoaldehyde **1b** (1 mmol) were treated with allene (1 bar), alanine methyl ester hydrochloride (1.2 mmol), NMM (1 mmol), $[Pd_2(dba)_3]$ (2.5 mol%), tris(2-furyl)phosphane (TFP) (10 mol%), and Cs_2CO_3 (4 equiv) in toluene at 100°C for 24 h (48 h for **1b**) to afford **10a** and **10b** in 69% and 57% yield, respectively (Table 1, entry 1). The configuration of **10a**, **b** was established by NOE studies. Phenylalanine methyl ester, aspartic acid methyl ester, and methionine methyl ester were successfully employed in the cascade reaction to give **11**–**13** in 54–57% yield (Table 1, entries 2–4). Interestingly phenylglycine methyl ester, under the same conditions, afforded **14**/**15** as a 3.5:1 mixture in 64% yield (Table 1, entry 5). The configuration of **14** and **15** was established by NOE studies and, in the case of the major isomer **15**, by an X-ray crystal structure (Figure 1). When the reaction was carried out at 100°C for 12 h, the crude product comprised a 12:12:1 mixture of cycloadducts **4** (R = Ph, X = I, Y = CH), **14**, and **15**. This indicates that **15** might



Scheme 1. Four-component cascade that begins with 2-iodoaryl aldehyde **1a** or 2-bromoaryl aldehyde **2b** and generates azomethine ylides, azomethine imines, and nitrones as integral parts of the cascade.

Table 1: Four-component azomethine ylide cycloaddition/allene insertion/nucleophile incorporation cascades with α-amino acid methyl esters.[a]

Entry	α Amino acid methyl ester	*t* [h]	Product	Yield [%]
1		24	 **10a,b**	69 (**10a**, Y = CH) 57[b] (**10b**, Y = N)
2		24	 **11a,b**	54 (**11a** Y = CH) 59[b] (**11a**, Y = N)
3		24	 **12**	57
4		24	 **13**	57
5		24	 **15** 1.0  **14** 3.5	64
6		24	 **16** : **17** 1 : 1	53

[a] All reactions were carried out in toluene at 100°C. [b] Reaction time 48 h.

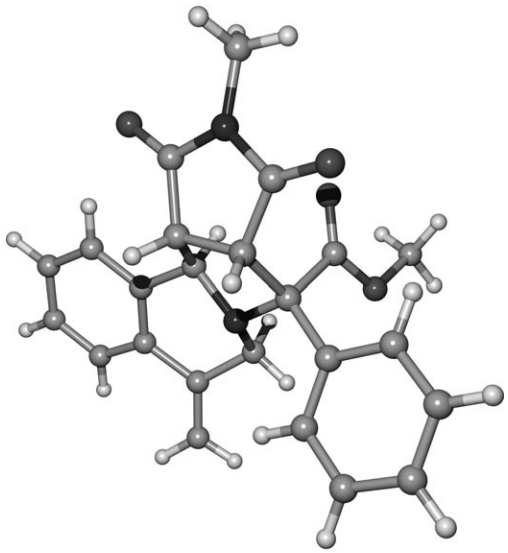
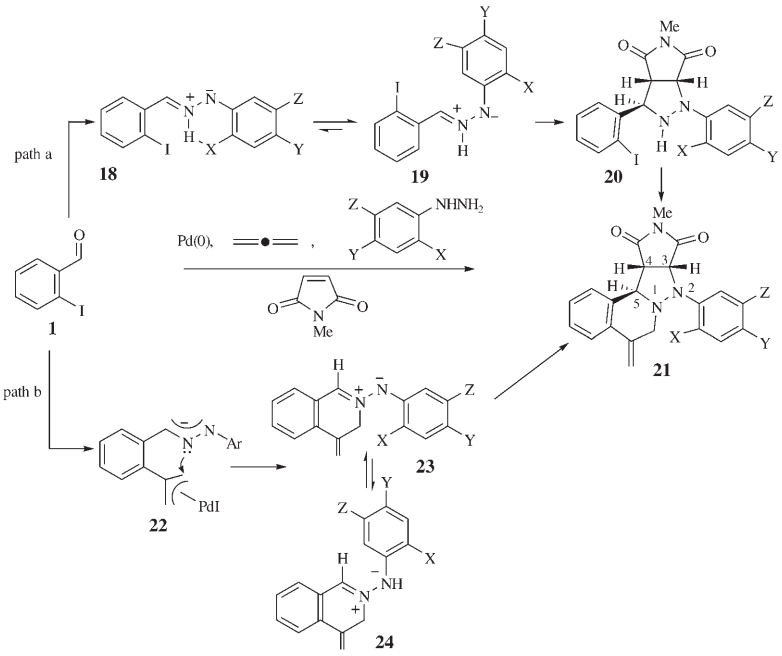


Figure 1. X-ray crystal structure of **15**.[15]

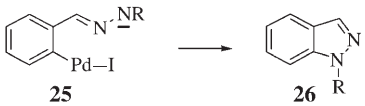
arise through epimerization of **14**, or alternatively, that **14** might undergo a slow retro-1,3-dipolar cycloaddition reaction to generate a new *syn* azomethine ylide **5** (R = Ph, Y = CH) in which the isoquinoline ring is present. The *syn* **5** ylide then equilibrates with *anti* azomethine ylide **6** (R = PH, Y = CH) followed by a 1,3-dipolar cycloaddition reaction through an *exo* transition state to give **15**. Similar results were obtained when the glycine methyl ester was employed in the above cascade (Table 1, entry 6). After 24 h, **16** and **17** were obtained as a 1:1 mixture. Further studies are clearly required to delineate the precise order and nature of the steps involved in this four-component cascade. Current evidence favors path a, which passes through compound **4**, as the configuration of the product conforms to that expected for processes that proceed via **3a**/**3b**.

In seeking to extend the cascade to azomethine imines, through the utilization of hydrazines in place of α-amino esters, we were cognizant of the fact that 1,2-prototropy in hydrazones generally requires temperatures of 120–150 °C.[10] We therefore evaluated a strategy that utilized intramolecular hydrogen bonding to proximal fluorides to stabilize the azomethine imine **18** (Scheme 2). Such hydrogen bonding appears to be weak (ca. 0.2 kcal mol^{-1}),[11] but might be enhanced by electrostatic effects.

Initially we surveyed the reactions of 2,5-difluorophenyl hydrazine and 2-fluorophenylhydrazine with **1**, NMM, and allene in toluene in the presence of a catalyst system that comprises $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), and Cs_2CO_3 (2 equiv). The four-component cascade products **21a** and **b** were obtained in 68 and 72% yield, respectively (Table 2, entries 1 and 2), but their configuration signaled that an *exo* transition state was involved. Azomethine imines impart an imperfect memory of dipole stereochemistry to the product owing to the absence of a fixed configuration at N2 in **21**. A similar pattern was displayed by 2-trifluoromethylphenyl hydrazine which afforded **21c** in 70% yield (Table 2, entry 3). In this case, hydrogen bonding would involve a seven-membered ring in **18**. Evaluation of other hydrazines (Table 2, entries 4–8) showed that the cascade proceeded in the absence of a proximal halogen (Table 2, entries 4 and 7) and that phenyl vinyl sulfone gave the four-component cascade product **21h** both regio- and stereoselectively (Table 2, entry 8). The structure of **21h** was unequivocally determined by X-ray crystallography (Figure 2). The phenyl and the 2,5-difluorophenyl rings are essentially parallel and approximately 3.5 Å apart, which suggests π stacking. AM 1 calculations of the activation energies for the cycloadditions of **18**, **19**, **23**, and **24** show that *exo* cycloadducts via **18** and **23** are favored, with the latter ($E_a = 19.11$ kcal mol^{-1}) favored over the former ($E_a = 22.75$ kcal mol^{-1}).[12] Hydrazones ArCH=N-NH-EWG (EWG = CO_2R, SO_2R) do not give four-component cascade products under our conditions, nor do we observe the formation of indazoles by cyclization of the palladium complex **25** to **26**.[13]

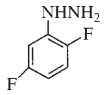
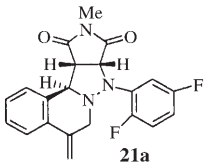
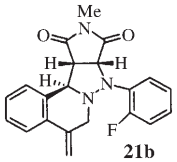
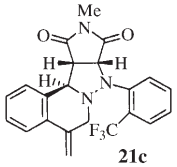
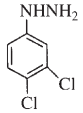
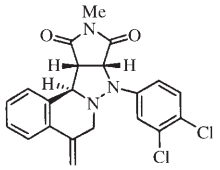
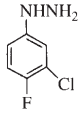
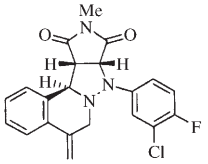
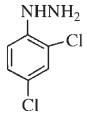
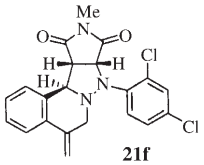
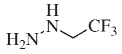
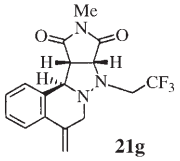
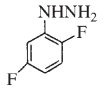
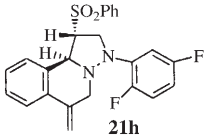


Scheme 2. The use of hydrazines in the extension of the cascade to azomethine imines.



Oxime anions exhibit ambident character (O versus N) with alkylating agents,[14] which prompted a study of their use in multicomponent cascade reactions. The example shown in Scheme 3 parallels the hydrazine case and affords **27** in 62% yield.

Table 2: Four-component azomethine imine cycloaddition/allene insertion/nucleophile incorporation cascades with hydrazines.[a]

Entry	Hydrazines	*t* [h]	Product	Yield [%]
1		24	 **21a**	68
2		24	 **21b**	72
3		24	 **21c**	70
4		24	 **21d**	63
5		24	 **21e**	66
6		24	 **21f**	58
7		24	 **21g**	53
8		24	 **21h**	55

[a] All reactions were carried out in toluene at 100 °C.

In conclusion, we have demonstrated novel four-component palladium catalyzed 1,3-dipolar cycloaddition/allene insertion/nucleophile incorporation cascades that proceed via intermediate azomethine ylides, azomethine imines, and nitrones. Imines undergo cycloaddition through an *endo* transition state prior to incorporation of the allene. The precise order of events in the case of hydrazines and hydroxylamines is not clear but may involve an initial incorporation of the allene followed by trapping of the π-allylpalladium species by the ambident hydrazone and oxime anions and finally cycloaddition through an *exo* transition state. Such a reversal in the relative rates of allene incorporation/cycloadduct formation would be consistent with the slower cycloaddition rates of hydrazones and oximes. These four-component cascades result in a substantial increase in molecular complexity with formation of five new bonds, two rings and two–four stereocenters.[16]

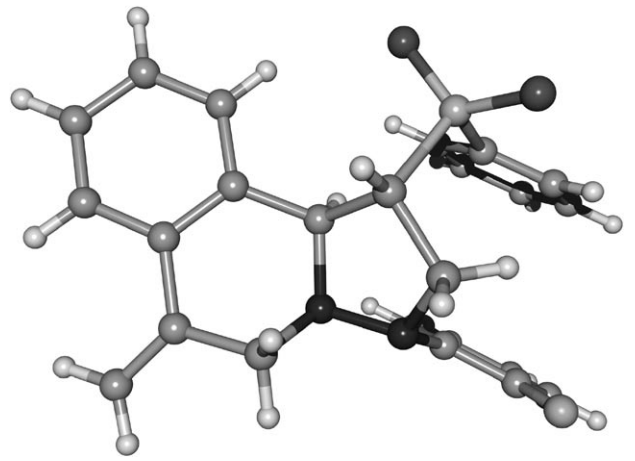
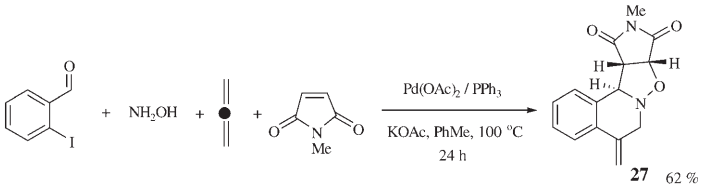


Figure 2. X-ray crystal structure of **21 h**.[15]



Scheme 3. Reactivity of oxime anions with alkylating agents in the multicomponent reaction.

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[15] Crystal data for $C_{24}H_{22}N_2O_4$ (**15**): $0.26 \times 0.15 \times 0.14\ mm^3$, $M = 402.44$, monoclinic, space group $P2_1/n$, $a = 10.6722(2)$, $b = 14.8397(3)$, $c = 13.0511(2)$ Å, $\beta = 109.1850(9)°$, $V = 1952.14(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.369\ mg\,m^{-3}$, $\mu = 0.094\ mm^{-1}$, $F(000) = 848$, $T = 150(2)$ K; data collection: $2.15 \le \theta \le 26°$; 3820 independent reflections were collected ($R_{int} = 0.0637$), 3322 reflections with $I > 2\sigma(I)$; structure refinement: number of parameters = 360; goodness of fit, $s = 1.017$, $wR_2 = 0.0979$, $R_1 = 0.0361$. Crystal data for $C_{24}H_{20}F_2N_2O_2S$ (**21h**): $0.30 \times 0.03 \times 0.03\ mm^3$, $M = 438.48$, orthorhombic, space group $Pna2_1$, $a = 31.7330(9)$, $b = 10.3570(2)$, $c = 6.16900(10)$ Å, $V = 2027.50(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.436\ mg\,m^{-3}$, $\mu = 0.203\ mm^{-1}$, $F(000) = 912$, $T = 150(2)$ K; data collection: $2.75 \le \theta \le 26°$; 3345 independent reflections were collected ($R_{int} = 0.119$); 2717 reflections with $I > 2\sigma(I)$; structure refinement: number of parameters = 280; goodness of fit, $s = 1.026$; $wR_2 = 0.1078$, $R_1 = 0.0457$. CCDC 273019 (**15**) and -273011 (**21h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] For general experimental procedures (Table 1, Table 2, and Scheme 3) and characterization data for selected compounds, see Supporting Information.

