Synthesis of Spiro Bis-Indanes via Domino Stetter–Aldol–Michael and Stetter–Aldol–Aldol Reactions: Scope and Limitations

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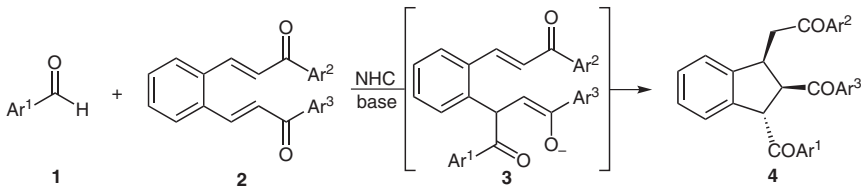
Abstract: The synthesis of spiro bis-indanes by means of N-heterocyclic carbene (NHC) catalysis is reported. The dimerization of various *o*-formylchalcone substrates or their combination with phthaldialdehyde derivatives under the catalysis of thiazolium-derived carbenes afforded Stetter–aldol–Michael products and Stetter–aldol–aldol products, respectively. The use of poor Michael acceptors in conjunction with an *N*-alkyltriazolium-derived catalyst furnished a variety of dibenzo[8]annulene products. This work highlights the interplay of a variety of factors affecting competing pathways in NHC-catalyzed domino reactions.

Key words: NHC, organocatalysis, Stetter, umpolung, domino reactions, Michael, aldol

In recent years, N-heterocyclic carbene (NHC)-catalyzed reactions have been the subject of intensive research.[1] In 2009, our group reported the diastereoselective synthesis of indanes via a domino[2] Stetter–Michael reaction.[3,4] We proposed that this reaction proceeds through the addition of an acyl anion equivalent derived from **1** onto an electron-poor olefin **2**, which generates an enolate intermediate **3** in situ. Subsequently, the enolate in **3** is trapped intramolecularly by a second electron-poor olefin to furnish the desired indane **4** (Scheme 1).

Following the success of this indane synthesis, we became interested in the application of this concept towards the synthesis of benzo[*b*]furans **7** via a domino acyloin–oxa-Michael reaction and isoindolines **8** via a domino aza-acyloin–aza-Michael reaction (Scheme 2a).[5] At the outset of our studies, we investigated both domino processes by employing furfural (**5**) and *o*-formylchalcone **6a**. Unfortunately, neither product **7** nor **8** were obtained. More interestingly, we obtained a complex spirocyclic structure **9a**, which is derived from two equivalents of **6a**. This exciting discovery allows the formation of three new carbon–carbon bonds and a quaternary center in one synthetic operation. The postulated mechanistic rationale for the formation of **9a** is similar to that of the synthesis of indanes (Scheme 2b). Once the acyl anion equivalent **I** is generated,[6] it attacks the electron-poor olefin portion of a second equivalent of **6a** leading to the formation of the enolate intermediate **II**. An aldol reaction then takes place,[7] along with elimination of the catalyst to furnish intermediate **III**. Under the basic reaction conditions, ketone **III** is deprotonated to form enolate intermediate **IV**, which cyclizes to **10a**. Finally, dehydration of this intermediate affords the spiro bis-indane product **9a**.

In late 2010, we disclosed this highly efficient synthesis of spiro bis-indanes.[8] This work began with studies aimed at finding the optimal reaction conditions and scope of the Stetter–aldol–Michael (SAM) reaction (Table 1). The first step consisted in screening the main families of NHCs (not shown), of which thiazolium salt **11** gave the best results at 30 mol% loading. In order to achieve the best yield and diastereocontrol in this transformation, we surveyed various bases and found 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to be optimum (Table 1, entries 1–5). Using this base, the catalyst loading could be reduced to 10 mol% without significantly affecting the yield or selectivity (entry 6). Having set the optimized conditions, the scope of the reaction was then studied. In general, aromatic ketone acceptors give excellent yield and diastereoselectivity (entries 6–8). Whereas electron-withdrawing groups on the aromatic ring provide a faster reaction and a decreased diastereomeric ratio, electron-donating substituents result in a slower and incomplete reaction, albeit with an improved diastereomeric ratio (entries 7, 8). We attribute the effect of the aromatic substituent on the diastereomeric ratio to a retro-Michael reaction that reduces the initially high diastereomeric ratio observed.[8] The reactivity of aryl ketone substrates is also greatly influenced by the type and position of the substit-



Scheme 1 NHC-catalyzed diastereoselective synthesis of indanes via a domino Stetter–Michael reaction

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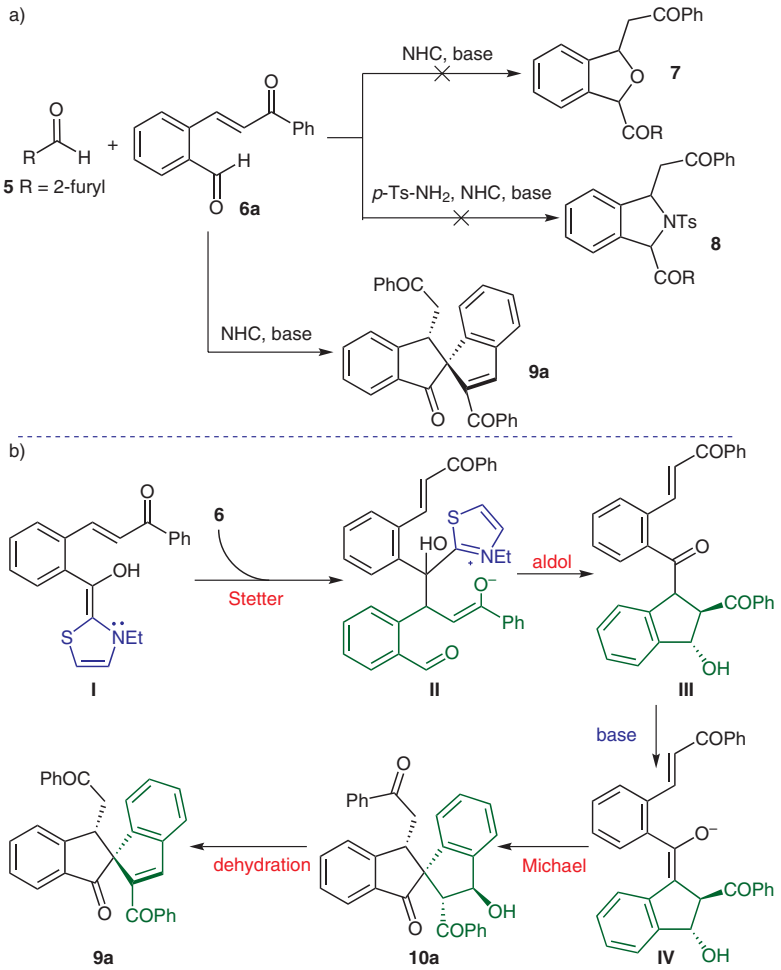
uent (R^1) incorporated on the left portion of the acceptor **6** (entries 9–12). The picture emerging from these results is that electron-withdrawing groups (relative to the aldehyde) accelerate the reaction. Particularly interesting are the results from entries 6 and 11 which show a faster reaction in the case of *p*-methoxy-substituted chalcone **6f**. These observations support the notion that formation of the Breslow intermediate **I** is slower than subsequent steps in the SAM sequence.

The use of aliphatic ketones results in good yield and moderate diastereoselectivity (entry 13). Finally, thioester acceptor **6i** afforded the bis spiro-indane product with good diastereoselectivity, but in a modest yield (entry 14). A screening of other families of acceptors revealed that esters, sulfones, and nitriles do not afford the desired product under our optimized conditions. Thus, the scope of the SAM reaction seems limited to ketone and thioester acceptors.

Based on our understanding of the SAM reaction mechanism, we developed an analogous Stetter–aldol–aldol (SAA) process. This proposed domino transformation relies on the reactivity of *o*-phthaldialdehydes, in which one formyl group would be involved in the Stetter reaction and the second formyl group would be involved in a second aldol ring-closing step. In order to test our hypothesis, we performed a model reaction employing *o*-phthaldialdehyde (**12a**) and *o*-formylchalcone **6a** that smoothly furnished SAA product **13**. Unfortunately, the product was obtained as an inseparable 1:1 mixture of diastereomers. Therefore, we decided to oxidize the diastereomeric mixture of alcohols to a single diketone **14** in order to facilitate the isolation and analysis of the product (Table 2). During the optimization of the reaction conditions, we also found that better yields could be obtained by employing two equivalents of acceptor **6**. In this manner, the SAA reaction could proceed to completion despite the competing SAM process forming dimer **9**.

The scope of the SAA reaction is shown in Table 2. The use of electron-withdrawing groups (EWGs) on the aryl ketone portion of the acceptor **6** is well tolerated (entry 2). In contrast, electron-donating groups (EDGs) considerably affect the rate of the reaction, resulting in a modest yield (entry 3). The use of EDGs on C3 of the acceptor **6f** (R^2 = 3-OMe) also showed a notable decrease in the reactivity, affording the product in poor yield (entry 4). On the other hand, acceptors **6d** and **6j** bearing EWGs enhanced the electrophilicity of the Michael acceptor, reducing the reaction time and increasing the yield of the product (entries 5 and 6). Finally, the effect of substituents on the *o*-



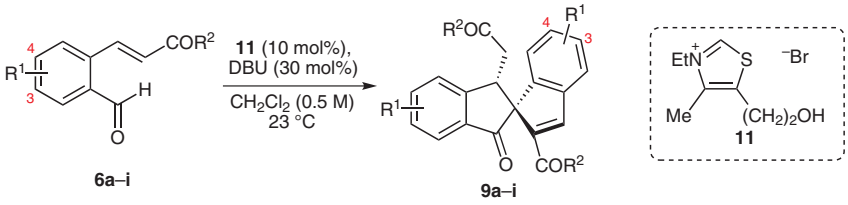
Scheme 2 a) Domino Stetter reaction; b) mechanistic rationale for the domino Stetter–aldol–Michael reaction

phthaldialdehyde partner was probed (entries 7 and 8). Interestingly, the use of methoxy-substituted dialdehyde substrate **12b** furnishes product **14g** as a single regioisomer prior to the oxidation step (entry 7). Again, this outcome can be attributed to the dual nature of alkoxy substituents as electron-donating and electron-withdrawing at the *para* and *meta* positions, respectively. Surprisingly, the use of electron-poor *o*-phthaldialdehyde substrate **12c** (R^1 = F) resulted in a very sluggish transformation, requiring the use of a highly reactive SAA partner in order to achieve a synthetically useful yield (entry 8).

Based on our experimental results in the SAM reaction, we could observe that *o*-formylchalcone derivatives **6a–i** were very reactive Stetter acceptors. Therefore, we decided to further study electron-withdrawing groups that are known for being less reactive in intermolecular Stetter reactions, such as esters and α-alkyl-α,β-unsaturated ketones.[1f]

We initiated our investigations by assessing the reactivity of ester substrate **16a** using standard conditions for the Stetter reaction. Unfortunately, the spiro bis-indane product **17a** was not obtained using either thiazolium salt **11** or triazolium salt **15** as precatalyst (Scheme 3a). This failure prompted us to explore a different type of NHC. In 2008, Enders and co-workers reported the use of the *N*-benzyl-substituted triazolium salt **18** in their asymmetric intermolecular Stetter reactions.[9] In their case, **18** was shown to be a more reactive NHC compared to other families of nucleophilic carbenes such as thiazolylidenes or *N*-aryltriazolylidenes. Unexpectedly, when **16a** was reacted with triazolium salt **18** a dibenzo[8]annulene product **19a** was obtained. Similarly, when sulfone **16b** and cyanide **16c** were reacted with catalysts **18** and **11**, respectively, dibenzo[8]annulenes **19b** and **19c**[10] were obtained.[11] These products presumably arise from sequential inter- and intramolecular Stetter reactions. We postulate that forma-

Table 1 Optimization and Scope of the Domino Stetter–Aldol–Michael (SAM) Reaction



Entry	R^1	R^2	Time (min)	Product[a]	Yield (%)[b,c]	dr[d]
1[e]	H	Ph	19 h	**9a**	(<10)	>20:1
2[f]	H	Ph	10	**9a**	n.r.[g]	–
3[h]	H	Ph	5 h	**9a**	(<5)	–
4[i]	H	Ph	45	**9a**	77	5:1
5[j]	H	Ph	35	**9a**	75	20:1
6	H	Ph	15	**9a**	79	17:1
7	H	4-ClC_6H_4	5	**9b**	86	12:1
8	H	4-$MeOC_6H_4$	45	**9c**	68	>20:1
9	4-F	Ph	5	**9d**	64	11:1
10	4-F	4-ClC_6H_4	15	**9e**	80	16:1
11	3-MeO	Ph	9	**9f**	85	>20:1
12	3-MeO	4-ClC_6H_4	5	**9g**	81	10:1
13	H	Me	195	**9h**	75	7:1
14	H	SEt	120	**9i**	31	13:1

[a] The relative configuration was determined by X-ray crystallography (see ref. 8).
[b] Combined yield of pure isolated product diastereomers.
[c] Numbers in parentheses represent conversion.
[d] Determined from ^{1}H NMR analysis of the crude reaction mixture.
[e] Conditions: 30 mol% of **11** and 1 equiv of *i*-Pr_2NEt.
[f] Conditions: 30 mol% of **11** and 27 mol% of tetramethylguanidine (TMG).
[g] n.r. = no reaction.
[h] Conditions: 10 mol% of **11** and 9 mol% of Cs_2CO_3.
[i] Conditions: 30 mol% of **11** and 1 equiv of DBU.
[j] Conditions: 30 mol% of **11** and 27 mol% of DBU.

tion of **19** is mainly driven by rapid protonation of intermediate **V** forming intermediate **VI**. Apparently, this process occurs more rapidly than the aldol ring closure leading to intermediate **VI′**. Subsequently, intermediate **VI** releases the NHC to give intermediate **VII**, which undergoes a second Stetter reaction to form the eight-membered ring **19a** (Scheme 3b).

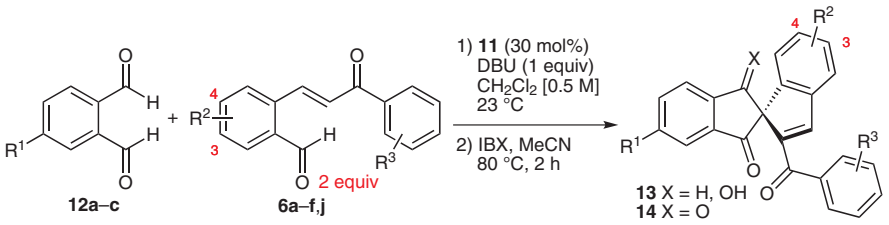
To date, it has been particularly difficult to perform intermolecular Stetter reactions on linear α-alkyl substituted Stetter acceptors.[12] This difficulty is presumably due to the reduced reactivity caused by the steric interaction of the α-alkyl substituent and the loss of conjugation between the α,β-double bond and the ketone. Knowing about the high reactivity of *o*-formylchalcone derivatives, we decided to investigate the use of substrate **20** with catalyst **11**. To our surprise, the dibenzo[8]annulene **21** was obtained in low yield (Scheme 4). In this case, the competing aldol step is probably slowed due to steric hindrance, thus leading to preferential protonation and subsequent formation of the eight-membered ring. Nevertheless, the most remarkable feature of this transformation is that sequential Stetter reactions occurred to form the C_2-symmetric diastereomers.

Motivated by the sequential Stetter reaction on **20**, we turned our attention to diketone **22** for use in the SAA reaction. This acceptor was expected to be less reactive in the SAA reaction due to the increased steric hindrance in both the Stetter and the first aldol steps. To this end, acceptor **22** was prepared and reacted with phthaldialdehyde (**12a**) (Scheme 5), affording the nondehydrated SAA adduct **23**. Despite the low yield, this transformation is noteworthy due to the stereoselective formation of four contiguous stereocenters. With the aim of improving the yield, several reaction parameters were varied such as the solvent (toluene, *N*,*N*-dimethylformamide, ethanol, and tetrahydrofuran), the catalyst (**11**, **18**), and even portionwise addition of catalyst **11**. However, no more than a trace amount of product was obtained in each case due to low conversion. Only when dichloroethane was used as solvent and by employing forcing conditions was it possible to obtain the desired product in low yield. The detection of only one diastereomer in the crude reaction mixture suggests a highly diastereoselective SAA reaction.

Another type of acceptor that was investigated was the double Michael acceptor **24**, which was previously employed in our synthesis of indanes.[4] We hypothesized this highly electrophilic acceptor would undergo a Stetter–Michael–aldol reaction in analogy to the SAA reaction (Scheme 6). Satisfyingly, the desired product was obtained in moderate yield as a single diastereomer, again indicating the possibility of selectively forming four contiguous stereocenters.

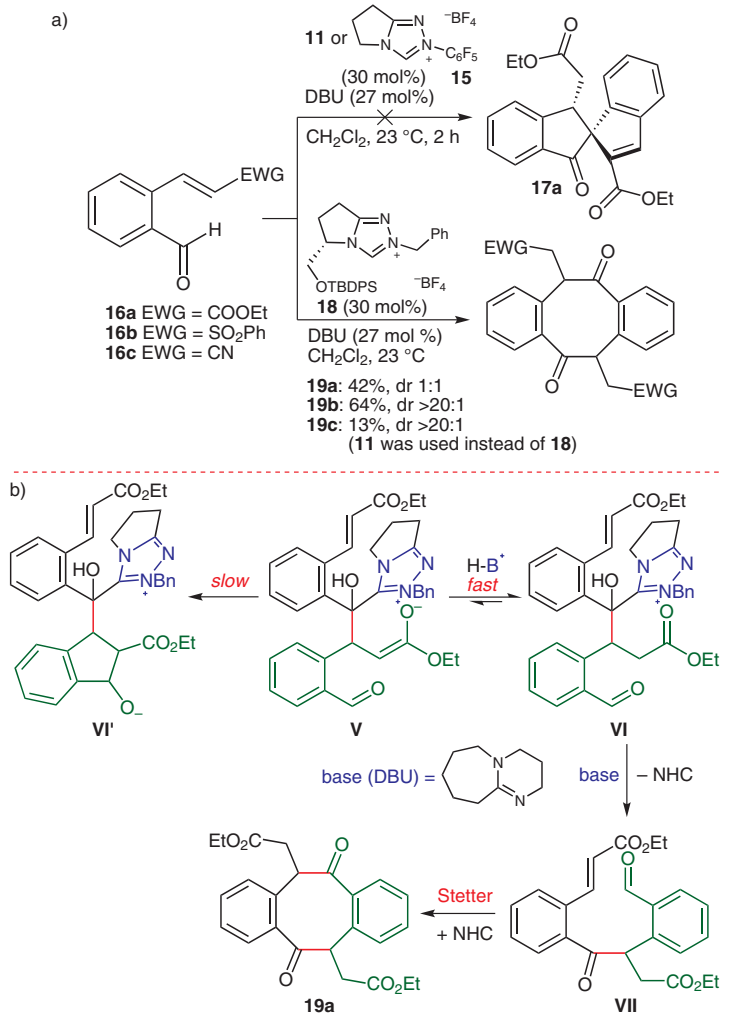
While studying the scope of the SAA reaction, we investigated the reactivity of ester acceptor **16a** with *o*-phthaldialdehyde (**12a**). When using catalyst **11**, no reaction was observed. In contrast, *o*-phthaldialdehyde (**12a**) was completely consumed and acceptor **16a** remained intact when catalyst **18** was used (Scheme 7a). The product isolated from the reaction mixture was found to be a dimer of **12a**. The same unidentified dimeric product was obtained when the reaction was performed with dialdehyde **12a**

Table 2 Domino Stetter–Aldol–Aldol (SAA) Reaction

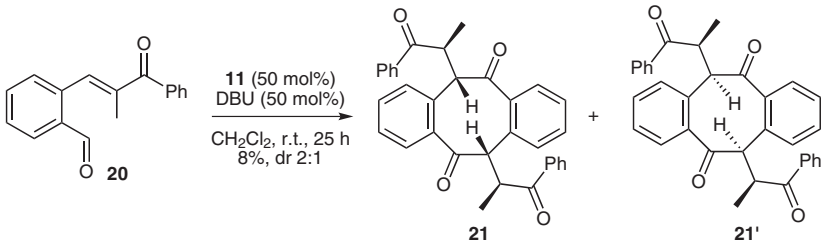


Entry	R^1	R^2	R^3	Time (min)[a]	Product	Yield (%)[b]
1[c]	H	H	H	20	**13a**	71
2	H	H	4-Cl	30	**14b**	58
3	H	H	4-OMe	60	**14c**	25
4	H	3-OMe	H	100	**14d**	36
5	H	4-F	H	5	**13e**	72
6	H	4-OMe	4-Cl	15	**14f**	75
7	OMe	H	H	35	**14g**	42
8	F	4-F	4-Cl	60	**14h**	50

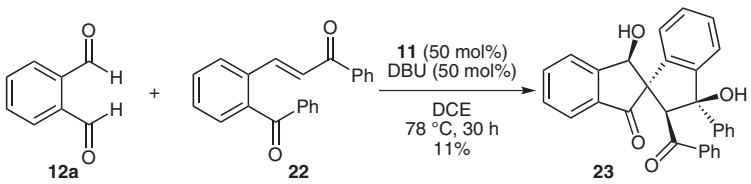
[a] Reaction time for the Stetter–aldol–aldol (SAA) step.
[b] Yield of pure isolated product.
[c] Reaction performed on a gram scale.
[d] Each diastereomer of products **13a** and **13e** was isolated prior to the oxidation step.



Scheme 3 a) Synthesis of dibenzo[8]annulenes **19a–c**; b) proposed mechanism for the synthesis of **19a**

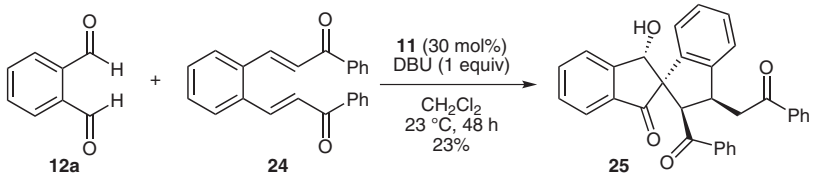


Scheme 4 C_2-Symmetric dibenzo[8]annulene products from α-methyl *o*-formylchalcone **20**[13]

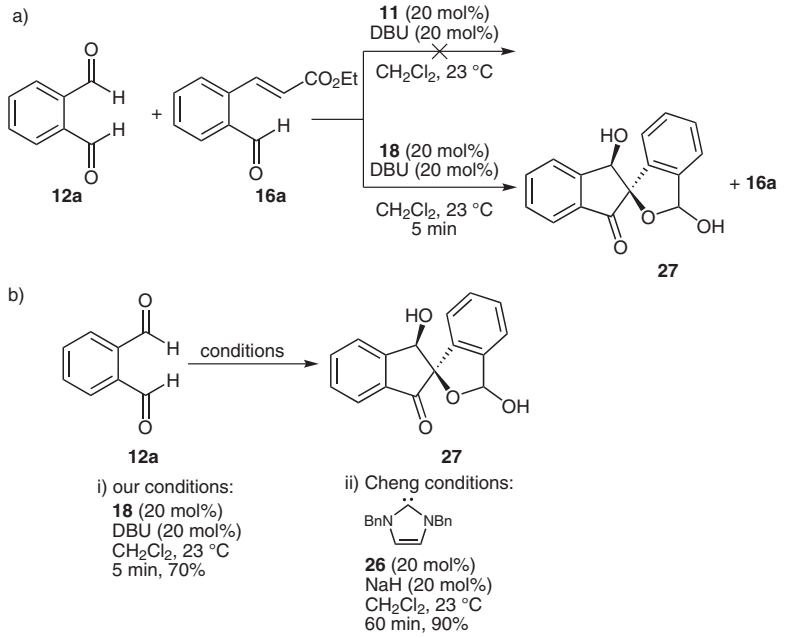


Scheme 5 Stetter–aldol–aldol reaction using benzoylchalcone **22**

alone with catalyst **18** (Scheme 7b). Very recently, Cheng and co-workers disclosed a dimerization of phthaldialdehydes catalyzed by *N*,*N*′-dibenzylimidazolylidene (**26**).[14] X-ray crystallography confirmed their structural assignment of the dimeric product as lactol **27**, whose NMR spectra matched those of our unknown product.



Scheme 6 Domino Stetter–Michael–aldol reaction



Scheme 7 Domino acyloin-aldol-aldol reaction

In conclusion, we have reported a series of highly efficient NHC-catalyzed domino transformations that allow the formation of three carbon–carbon bonds and up to four contiguous stereogenic centers. Various Michael acceptors were surveyed for the domino SAM and SAA reactions. Thioesters and ketones were shown to lead to the desired spiro bis-indane products in contrast to esters, sulfones, and nitriles. Under appropriate conditions, these and other weaker acceptors led to dibenzo[8]annulene products via a double Stetter sequence. A highly diastereoselective domino Stetter–Michael–aldol reaction was also demonstrated for the first time. Taken together, these results show the importance of subtle variations in the reaction conditions on the outcome of domino NHC-catalyzed reactions.

TLC was performed on Merck Silica Gel 60 F254 and was visualized with UV light and 5% phosphomolybdic acid (PMA). Silica gel SI 60 (40–63 μm) used for column chromatography was purchased from Silicycle Chemical Division. NMR spectra were measured in $CDCl_3$ solution at 500 MHz for ^1H and 125 MHz for ^{13}C. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards for chemical shifts. High-resolution mass spectra (HRMS) were obtained on a double focusing high-resolution spectrometer. EI ionization was accomplished at 7 eV. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. All samples were prepared as a film on a KBr disc or pellet using KBr (IR grade) for IR analysis. Melting points were measured in a melting point apparatus and are uncorrected. Anhydrous solvents were dried using a Braun Solvent Purification System and stored under N_2 over 3 Å molecular sieves.[15] Unless otherwise noted, commercially available reagents were used without further purification. All reactions were carried out under an inert atmosphere.

Spiro Bis-Indanes via Domino SAM; General Procedure

To a stirred a solution of aldehyde **6a–i** (1 equiv) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium bromide (**11**; 0.1 equiv) in anhyd CH_2Cl_2 (0.5 M) placed in a 5 mL oven-dried Schlenk tube fitted with a septum was added DBU (0.3 equiv). After stirring the mixture at r.t. for the time indicated in Table 1, the reaction was quenched with sat. aq NH_4Cl (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were filtered through a small pipette column containing anhyd Na_2SO_4/silica gel, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography employing the indicated eluent.

rel-(1′*R*,3*S*)-2′-Benzoyl-3-(2-oxo-2-phenylethyl)-1,2′-spirobi[inden]-1(3*H*)-one (9a) (Major Diastereomer)

Reaction carried out on 0.21 mmol scale; yield: 67 mg (79%); dr = 17:1; white crystals; mp 187–189 °C, R_f = 0.25 (30% EtOAc in hexanes).

IR (KBr film): 1716, 1682, 1629 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.97–7.91 (m, 3 H), 7.72 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1 H), 7.63–7.60 (m, 1 H), 7.59–7.53 (m, 3 H), 7.61–7.54 (m, 3 H), 7.53–7.48 (m, 4 H), 7.47–7.43 (m, 1 H), 7.37 (d, *J* = 7.3 Hz, 1 H), 7.32–7.27 (m, 2 H), 7.19 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1 H), 7.13 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1 H), 6.82 (d, *J* = 7.5 Hz, 1 H), 4.93 (dd, *J* = 9.3, 5.3 Hz, 1 H), 3.41 (dd, *J* = 17.1, 9.3 Hz, 1 H), 3.34 (dd, *J* = 17.1, 5.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.8, 197.6, 191.6, 155.4, 148.6, 145.5, 144.7, 143.7, 138.9, 137.3, 136.8, 135.4, 133.1, 132.2, 129.5, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 125.5, 125.4, 125.0, 72.4, 40.6, 39.1.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{32}H_{22}O_3$: 454.1569; found: 454.1566.

Spiro Bis-indanes via Domino SAA; General Procedure

To a stirred a solution of phthaldialdehyde **12a–c** (1 equiv), *o*-formylchalcone derivative **6a–f**, **j** (2 equiv), and **11** (0.3 equiv) in anhyd CH_2Cl_2 (0.5 M) in a 5 mL oven-dried Schlenk tube fitted with a septum was added DBU (1 equiv). After stirring the mixture at r.t. for the indicated time, the reaction was quenched with sat. aq NH_4Cl (4 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were filtered through a small pipette column containing anhyd Na_2SO_4/silica gel. The solvent was removed in vacuo. The crude product was purified by flash column chromatography employing the indicated eluent.

rel-(1*R*,1′*R*)-2′-Benzoyl-1-hydroxy-1,2′-spirobi[inden]-3(1*H*)-one (13a)

Reaction carried out on 3.7 mmol scale; yield: 432 mg (33%); dr = 1:1.1; light yellow crystals; mp 152–154 °C; R_f = 0.35 (10% EtOAc in toluene).

IR (KBr pellet): 3421, 3066, 1716, 1552, 1341, 1064, 758 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.6 Hz, 1 H), 7.84–7.80 (m, 4 H), 7.73 (s, 1 H), 7.60–7.56 (m, 3 H), 7.47 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.37 (dd, *J* = 7.4, 7.4 Hz, 1 H), 7.31 (dd, *J* = 7.4, 7.4 Hz, 1 H), 6.98 (d, *J* = 7.4 Hz, 1 H), 5.74 (d, *J* = 12.0 Hz, 1 H), 4.43 (d, *J* = 12.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.3, 195.6, 155.5, 149.4, 149.3, 141.9, 138.5, 136.2, 135.8, 132.9, 129.9, 129.6, 128.6, 128.5, 126.6, 125.2, 124.7, 121.8, 77.4, 74.3.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{24}H_{16}O_3$: 352.1099; found: 352.1100.

rel-(1*S*,1′*R*)-2′-Benzoyl-1-hydroxy-1,2′-spirobi[inden]-3(1*H*)-one (*epi*-13a)

Yield: 492 mg (38%); light pink crystals; mp 241–244 °C; R_f = 0.15 (10% EtOAc in toluene).

IR (KBr pellet): 3428, 1690, 1621, 1553, 1343, 1292, 727 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.86 (d, *J* = 7.6 Hz, 2 H), 7.81 (dd, *J* = 7.3, 7.6 Hz, 1 H), 7.75 (s, 1 H), 7.61–7.57 (m, 3 H), 7.50 (dd, *J* = 7.7, 7.7 Hz, 2 H), 7.37 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.23 (dd, *J* = 7.6, 7.6 Hz, 1 H), 6.77 (d, *J* = 7.6 Hz, 1 H), 6.07 (d, *J* = 9.2 Hz, 1 H), 1.96 (dd, *J* = 9.2, 6.7 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.8, 191.5, 154.0, 147.1, 146.6, 144.1, 143.5, 138.7, 136.9, 135.7, 132.4, 129.5, 129.2, 129.1, 129.0, 128.6, 125.9, 125.8, 124.8, 123.1, 75.6, 73.6.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{24}H_{16}O_3$: 352.1099; found: 352.1095.

Diethyl 2,2′-(3,4,7,8-Tetrahydrodibenzo[8]annulene)diacetate (19a); Typical Procedure

A flame-dried Schlenk tube was charged with (*E*)-ethyl 3-(2-formylphenyl)acrylate (**16a**; 50 mg, 0.24 mmol, 1 equiv) and (*S*)-2-benzyl-5-[(*tert*-butyldiphenylsilyloxy)methyl]-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate (**18**;[9] 40 mg, 0.072 mmol, 0.3 equiv). The tube was evacuated three times and refilled with dry N_2, and then the solids were dissolved in CH_2Cl_2 (0.24 mL, 1 M). Lastly, DBU (9.7 μL, 0.065 mmol, 0.27 equiv) was added to the solution at r.t. The reaction was monitored by TLC (20% EtOAc in hexanes). Upon completion (10 min), it was quenched with sat. aq NH_4Cl (0.5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic layers were filtered through a short pipette plug of anhyd Na_2SO_4/silica gel. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (20% EtOAc in hexanes) to furnish the title product as an inseparable mixture of diastereomers (dr = 5.3:1) in 42% yield (41 mg) as colorless needle-like crystals; mp 135–139 °C; R_f = 0.28 (20% EtOAc in hexanes).

IR (KBr film): 2980, 1725, 1714, 1490, 1094 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (major diastereomer) = 7.36 (d, *J* = 7.5 Hz, 2 H), 7.31 (dd, *J* = 7.3, 7.3 Hz, 2 H), 7.24 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 2 H), 7.10 (d, *J* = 7.2 Hz, 2 H), 5.75 (dd, *J* = 9.3, 4.5 Hz, 2 H), 4.20 (dddd, *J* = 7.2, 2.1, 2.0, 1.8 Hz, 4 H), 3.10 (dd, *J* = 15.1, 9.4 Hz, 2 H), 2.59 (dd, *J* = 15.2, 4.6 Hz, 2 H), 1.24 (dd, *J* = 7.2, 7.2 Hz, 6 H); δ (minor diastereomer) = 7.37 (d, *J* = 7.5 Hz, 2 H), 7.32–7.39 (m, 2 H), 7.26–7.22 (m, 2 H), 7.09 (d, *J* = 7.4 Hz, 2 H), 5.70 (dd, *J* = 9.4, 4.7 Hz, 2 H), 4.22–4.16 (m, 4 H), 3.14 (dd, *J* = 14.9, 9.4 Hz, 2 H), 2.76 (dd, *J* = 14.9, 4.7 Hz, 2 H), 1.20 (dd, *J* = 7.2, 7.2 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (major diastereomer) = 170.4, 132.0, 131.6, 128.6, 128.1, 126.9, 124.1, 120.3, 74.4, 60.9, 39.9, 14.4.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{24}H_{24}O_6$: 408.1572; found: 408.1575.

2,2′-Bis(phenylsulfonylmethyl)(3,4,7,8-tetrahydrodibenzo[8]annulene) (19b)

Following the typical procedure for **19a**, the reaction was performed with (*E*)-2-[2-(phenylsulfonyl)vinyl]benzaldehyde (**16b**; 50 mg, 0.18 mmol, 1 equiv) and **18**[9] (31 mg, 0.055 mmol, 0.3 equiv) in CH_2Cl_2 (0.37 mL, 0.5 M) and DBU (7.5 μL, 0.05 mmol, 0.27 equiv) for 10 min. The crude product was filtered and rinsed with CH_2Cl_2 (6 × 5 mL) to furnish the title product as an off-white solid (dr = >20:1) in 64% yield (32 mg); R_f = 0.20 (30% EtOAc in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (dd, *J* = 7.6, 7.6 Hz, 4 H), 7.75 (q, *J* = 7.2, 7.2, 7.2 Hz, 2 H), 7.64 (dd, *J* = 7.2, 7.2 Hz, 4 H), 7.25–7.25 (m, 6 H), 7.02–7.00 (m, 2 H), 3.65–3.54 (m, 4 H).

2,2′-(3,4,7,8-Tetrahydrodibenzo[8]annulene)diacetonitrile (19c)

Following the typical procedure for **19a**, the reaction was performed with (*E*)-3-(2-formylphenyl)acrylonitrile (**16c**; 25 mg, 0.15 mmol, 1 equiv) and **11** (12 mg, 0.048 mmol, 0.3 equiv) in CH_2Cl_2 (0.32 mL, 0.5 M) and DBU (6.4 μL, 0.04 mmol, 0.27 equiv) for 90 min. The crude product was purified by flash column chromatography to furnish the title product as a light yellow oil (dr = >20:1) in 13% yield (3.2 mg); R_f = 0.25 (30% EtOAc in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.6 Hz, 2 H), 7.78 (dd, *J* = 7.6, 7.4 Hz, 2 H), 7.67 (dd, *J* = 8.2, 7.6 Hz, 4 H), 5.67 (dd, *J* = 6.4, 5.7 Hz, 2 H), 3.10 (dd, *J* = 16.8, 5.1 Hz, 2 H), 2.94 (dd, *J* = 16.8, 7.0 Hz, 2 H).

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{20}H_{14}N_2O_2$: 314.1055; found: 314.1048.

2,2′-(3,4,7,8-Tetrahydrodibenzo[8]annulene)bis(1-phenylpropan-1-one) (21)

Following the typical procedure for **19a**, the reaction was performed with (*E*)-2-(2-methyl-3-oxo-3-phenylprop-1-enyl)benzaldehyde (**20**; 50 mg, 0.20 mmol, 1 equiv) and **11** (25 mg, 0.10 mmol, 0.5 equiv) in CH_2Cl_2 (0.24 mL, 1 M) and DBU (15 μL, 0.10 mmol, 0.5 equiv) for 25 h. The crude product was purified by flash column chromatography (20% EtOAc in hexanes) to furnish the title product as an inseparable mixture of diastereomers (dr = 2:1) in 8% yield (8.3 mg) as a light yellow oil; R_f = 0.3 (20% EtOAc in hexanes)

IR (KBr film): 2979, 2938, 1766, 1680, 1287, 1216, 972, 702 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (major diastereomer) = 7.99 (d, *J* = 7.1 Hz, 2 H), 7.93–7.87 (m, 4 H), 7.68 (d, *J* = 4.5 Hz, 2 H), 7.63–7.46 (m, 8 H), 7.33 (d, *J* = 7.8 Hz, 2 H), 5.91, (d, *J* = 8.8 Hz, 2 H), 3.68 (ddd, *J* = 15.8, 7.1, 7.1, 7.1 Hz, 2 H), 1.54 (d, *J* = 7.0 Hz, 6 H); δ (minor diastereomer) = 7.93–7.87 (m, 6 H), 7.63–7.46 (m, 12 H), 5.97 (d, *J* = 5.1 Hz, 2 H), 4.10 (ddd, *J* = 12.3, 5.1, 5.1, 5.1 Hz, 2 H), 1.10 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (major diastereomer) = 201.5, 170.3, 149.1, 135.9, 134.4, 134.0, 129.6, 129.1, 128.6, 126.2, 125.9, 123.4, 82.3, 47.1, 16.3.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{34}H_{28}O_4$: 500.1987; found: 500.1987.

2′-Benzoyl-1,3′-dihydroxy-3′-phenyl-2′,3′-dihydro-1,2′-spirobi[inden]-3(1*H*)-one (23)

A flame-dried Schlenk tube was charged with (*E*)-3-(2-benzoylphenyl)-1-phenylprop-2-en-1-one (**22**; 50 mg, 0.16 mmol, 1 equiv), *o*-phthaldialdehyde (**12a**; 32.2 mg, 0.24 mmol, 1.5 equiv), and **11** (20.2 mg, 0.08 mmol, 0.5 equiv) in 1,2-dichloroethane (0.16 mL, 1 M). The mixture was heated to 78 °C, and then DBU was added (12 μL, 0.08 mmol, 0.5 equiv) and heated for 30 h. The reaction was quenched with sat. aq NH_4Cl (0.5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 2 mL) and filtered through a short pipette plug of anhyd Na_2SO_4/silica gel. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (30% EtOAc in hexanes) to furnish the title product in 11% yield (7.7 mg) as an orange solid; mp 191–194 °C; R_f = 0.22 (30% EtOAc in hexanes).

IR (KBr film): 3412, 3061, 1715, 1605, 1447, 1218, 957, 735, 713 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.4 Hz, 2 H), 7.80 (d, *J* = 7.8 Hz, 1 H), 7.78 (d, *J* = 7.8 Hz, 1 H), 7.71 (dd, *J* = 7.4, 7.4 Hz, 1 H), 7.62 (d, *J* = 7.3 Hz, 2 H), 7.48 (dd, *J* = 7.3, 7.3 Hz, 1 H), 7.46 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.37 (dd, *J* = 7.4, 7.4 Hz, 2 H), 7.33 (dd, *J* = 7.7, 7.7 Hz, 2 H), 7.28 (dd, *J* = 7.3, 7.3 Hz, 1 H), 7.24 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.17 (ddd, *J* = 7.6, 1.1, 1.0, 1.0 Hz, 1 H), 6.98 (d, *J* = 7.5 Hz, 1 H), 6.65 (s, 1 H), 6.57 (d, *J* = 7.6 Hz, 1 H), 5.43 (s, 1 H), 5.34 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.7, 201.7, 153.5, 147.3, 143.7, 142.3, 136.9, 136.3, 135.8, 134.6, 129.5, 129.3, 128.9, 128.8, 128.5, 127.8, 126.5, 126.4, 124.6, 124.3, 123.8, 86.7, 72.7, 70.6, 59.0.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{30}H_{22}O_4$: 446.1518; found: 446.1512.

2′-Benzoyl-1-hydroxy-3′-(2-oxo-2-phenylethyl)-2′,3′-dihydro-1,2′-spirobi[inden]-3(1*H*)-one (25)

A flame-dried Schlenk tube was charged with (2*E*,2′*E*)-3,3′-(1,2-phenylene)bis(1-phenylprop-2-en-1-one) (**24**;[3] 50 mg, 0.15 mmol, 1 equiv), *o*-phthaldialdehyde (**12a**; 20.1 mg, 0.15 mmol, 1 equiv), and **11** (11.3 mg, 0.045 mmol, 0.3 equiv). The tube was evacuated three times and refilled with dry N_2, the solids were dissolved in CH_2Cl_2 (0.3 mL, 0.5 M) followed by the addition of DBU (22.4 μL, 0.15 mmol, 1 equiv) at r.t. The reaction was monitored by TLC (30% EtOAc in hexanes). When no further change was observed (48 h), the reaction was quenched with sat. aq NH_4Cl (0.5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 2 mL) and filtered through a short pipette plug of anhyd Na_2SO_4/silica gel. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (30% EtOAc in hexanes) to furnish the title product in 23% yield (16 mg) as a light yellow solid; mp 167–169 °C; R_f = 0.25 (30% EtOAc in hexanes).

IR (KBr film): 3485, 3062, 1713, 1681, 1596, 1579, 1217, 752, 690 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.8 Hz, 2 H), 7.97 (d, *J* = 10.4 Hz, 2 H), 7.80–7.76 (m, 2 H), 7.73 (dd, *J* = 7.4, 7.4 Hz, 1 H), 7.59–7.52 (m, 2 H), 7.51–7.41 (m, 5 H), 7.33 (d, *J* = 7.5 Hz, 1 H), 7.24 (dd, *J* = 7.4, 7.4 Hz, 1 H), 7.04 (dd, *J* = 7.4, 7.4 Hz, 1 H), 6.44 (d, *J* = 7.7 Hz, 1 H), 5.18 (d, *J* = 3.8 Hz, 1 H), 4.79 (d, *J* = 4.8 Hz, 1 H), 4.45 (ddd, *J* = 13.4, 10.0, 5.3 Hz, 1 H), 3.78 (dd, *J* = 17.6, 8.3 Hz, 1 H), 3.71 (dd, *J* = 17.6, 5.5 Hz, 1 H), 2.89 (d, *J* = 4.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.2, 201.8, 198.9, 153.7, 146.5, 139.7, 137.1, 135.8, 135.1, 133.9, 133.4, 129.5, 129.2, 129.1, 128.8, 128.4, 127.2, 125.7, 125.3, 125.1, 124.3, 73.6, 73.4, 55.8, 46.0, 45.4.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{32}H_{24}O_4$: 472.1674; found: 472.1675.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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