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Highly Stereoselective Synthesis of 1,2,3-Trisubstituted Indanes via Oxidative *N*-Heterocyclic Carbene-Catalyzed Cascades

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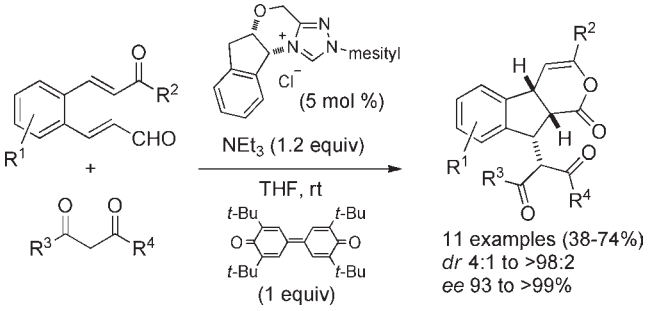
ABSTRACT



Three stereocenters are formed in the carbene catalyzed cascade reaction of enals with various β-diketones to give the corresponding indane derivatives with excellent stereoselectivities. The products are readily transformed to the corresponding 1,2,3-trisubstituted indane derivatives, which represent privileged substructures in medicinal chemistry.

Indenes[1] and indanes[2] have found widespread application as biologically important substructures in medicinal chemistry. Despite the high importance of these substance classes, surprisingly only few methods for their stereoselective synthesis have been reported.[3,4] Herein, we disclose a new approach to the synthesis of highly enantioenriched 1,2,3-trisubstituted indanes via oxidative NHC-catalysis (NHC = *N*-heterocyclic carbene).[5]

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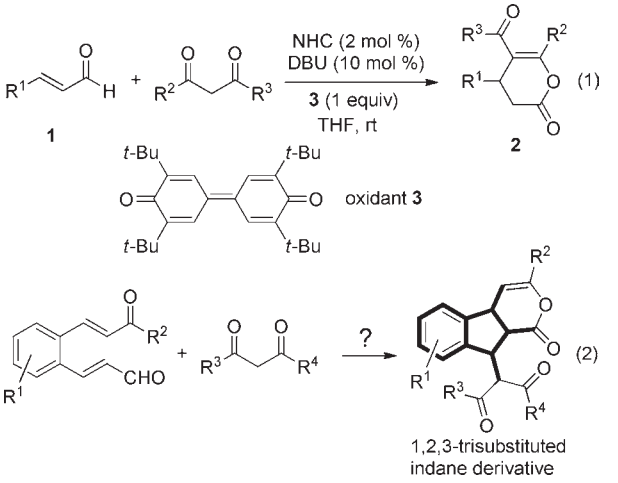
We recently showed that Breslow intermediates, readily generated by reaction of aldehydes with an NHC,[5] can be oxidized with mild organic oxidants to acylazolium ions, which react with various O-nucleophiles to the corresponding esters.[6–8] Furthermore, we published that α,β-unsaturated acylazolium ions, generated by NHC-catalyzed redox activation of enals **1** using oxidant **3**, react as Michael acceptors with β-diketones or β-ketoesters to give dihydropyranones **2** in good to excellent yields under mild conditions (Scheme 1, eq 1).[9–11]

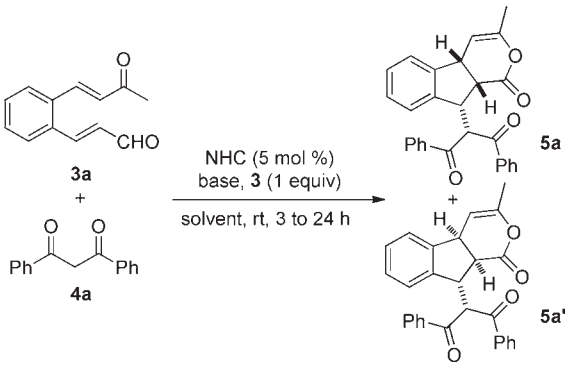
Scheme 1. NHC-Catalyzed Oxidative Cascade Reactions



Encouraged by these results we decided to apply redox activation of enals for the construction of the core structure of highly substituted indanes (eq 2).[4] The planned cascade reaction comprises two C–C-bond forming processes along with an intramolecular acylation. The challenging task was the control of the relative as well as absolute configuration of the 3 newly formed contiguous stereogenic centers.

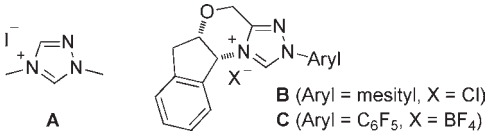
Test reactions were conducted with aldehyde **3a** and β-diketone **4a** to give indane derivatives **5a/5a′** at room temperature under different conditions. Using achiral triazolium salt **A** as catalyst precursor and Et_3N in THF provided only a low yield of the targeted product that was formed as a 1:1 mixture of diastereoisomers (Table 1, entry 1). With DBU reaction was faster and higher yielding

Table 1. Reaction of enal **3a** with **4a** under various conditions



entry	NHC	solvent (time h)	base (equiv)	yield (%)	*dr*[a] **5a:5a'**	*ee*[b] (%)
1	**A**	THF (15)	Et_3N (1.2)	10	1:1	
2	**A**	THF (3)	DBU (1.1)	30	<1:99	
3	**B**	THF (3)	DBU (1.1)	40	<1:99	89
4	**B**	THF (3)	DBU (0.3)	38	<1:99	89
5	**B**	THF (12)	Et_3N (0.3)	30	1:1	>99
6	**B**	PhMe (16)	Et_3N (0.1)	74	4.2:1	>99
7	**B**	PhMe (16)	Et_3N (1.2)	62	2.7:1	>99
8	**B**	PhMe (24)	KO*t*Bu (1.2)			
9	**B**	PhMe (24)	DABCO (1.2)	32	4:1	>99
10	**B**	DCM (24)	Et_3N (1.2)	26	>99:1[c]	>99
11	**C**	PhMe (24)	Et_3N (0.3)			

[a] Determined on isolated separated isomers. [b] Determined by HPLC using a chiral column. [c] Unidentified side product formed.



(entry 2). Interestingly, only isomer **5a′** was isolated in that case. We then switched to chiral triazolium salt **B**[12] as precatalyst and noted a further increase in yield (entry 3). Pleasingly, an acceptable enantioselectivity (89%) was achieved. A similar result was obtained upon lowering the amount of base (entry 4). Switching to NEt_3 lead to excellent enantioselectivity (ee >99%, entry 5). Reaction was slower and both diastereoisomers were isolated with very high enantioselectivity (the other enantiomer was not identified by HPLC analysis for both isomers). The relative configuration of the major isomer **5a** (*cis*,*cis*) was unambiguously assigned by X-ray analysis and NOE experiments and the relative configuration of **5a′** (*trans*,*cis*) was determined by NOE-experiments (see Supporting Information). The best yield was achieved in toluene (74%, entry 6). Diastereoselectivity was moderate but enantioselectivity was excellent. Increasing the amount of NEt_3 further lowered the diastereoselectivity (entry 7). KO*t*Bu did not work as base whereas with 1,4-diazabicyclo-[2.2.2]octane (DABCO) a lower yield was achieved, while

(8) NHC catalyzed oxidative esterification using MnO_2 as oxidant: (a) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Tetrahedron* **2009**, *65*, 3102. Using organic oxidants: (b) Noonan, C.; Baragwanath, L.; Connon, S. J. *Tetrahedron Lett.* **2008**, *49*, 4003. (c) Rose, C. A.; Zeitler, K. *Org. Lett.* **2010**, *12*, 4552.

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(11) (a) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176. (b) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2011**, *133*, 4694. Alternative mechanism: (c) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810. (d) Mahatthananchai, J.; Zheng, P.; Bode, J. W. *Angew. Chem., Int. Ed.* **2011**, *50*, 1673.

(12) Struble, J. R.; Bode, J. W. *Org. Synth.* **2010**, *87*, 362.

keeping the excellent enantioselectivity (entries 8, 9). Interestingly, in dichloromethane (DCM) isomer **5a** was the only isomer detectable, however, yield was low (entry 10). Surprisingly, with triazolium salt **C**[13] as precatalyst, the reaction did not work (entry 11)

We then tested the substrate scope of the cascade reaction under optimized conditions (toluene, NEt_3, **B** (5 mol %), 16 h). Since some nucleophiles reacted sluggishly using 0.1 or 0.3 equiv of NEt_3, all following experiments were conducted with 1.2 equiv of base. The enal and also the β-diketo component were varied and the relative configuration of products **5b**−**k** was assigned in analogy to **5a** (note that in the ^{1}H NMR spectrum, the vinylic proton of these compounds showed a very characteristic chemical shift for both isomers **5x** (*cis*,*cis*, around 5.4 ppm) and **5x′** (*trans*,*cis*, around 5.1 ppm)). Reaction of enal **3a** with acetylacetone delivered **5b** in 69% yield with high diastereoselectivity and excellent enantioselectivity (Figure 1). With β-arylenals bearing a halogen atom at the arene moiety, the cascade process delivered products **5c** and **5d** as single diastereoisomers in enantiomerically pure form. The *trans*,*trans*-isomers **5c′** and **5d′** were not identified by ^{1}H NMR spectroscopy in these reactions. A similar result was obtained using the naphthyl substituted enal (see **5e**). Yield was lower for reaction of acetylacetone with a more electron rich β-arylenal (38%, **5f**). For this compound, the other enantiomer was also identified (93% ee). The R^2-substituent in the enal (see eq 2 in Scheme 1) can also be varied. We replaced the methyl group by a phenyl substituent and noticed a far slower cascade process. Reaction time had to be extended to 24 h, and **5g** was isolated as a single isomer in 44% yield. As compared to the cascade conducted with acetylacetone, the ethyl substituted β-diketone congener reacted with enal **3a** with higher selectivity (**5h**: 54%) but the bis-*p*-tolyl-β-diketone ketone provided a moderate diastereoselectivity in a lower yield (**5i**). Because of solubility problems, reaction time was increased to 30 h for this nucleophile.

As expected, in the reaction of **3a** with an unsymmetrical β-diketone, the stereogenic center at the α-position to the β-diketone was not controlled (*dr* = 1.3:1, see **5j**). β-Ketoesters turned out to be suitable substrates as shown for a single example (**5k**). The *cis*/*trans*-selectivity at the ring was well controlled; however, the additional center α to the ester functionality was formed with low selectivity.

For assignment of the absolute configuration we studied the reaction of cinnamaldehyde with β-ketoester **6** under similar conditions to give dihydropyranone **7** in 69% yield with 92% ee (Scheme 2). Treatment of **7** with aq. HCl in refluxing dioxane led to ring-opening of the dihydropyranone; hydrolysis of the ester followed by decarboxylation gave the corresponding acid. Esterification with TMS-diazomethane eventually afforded known ester (*S*)-**8** in 88% yield ($[\alpha]_D$ = −23.6° (c = 1.0 in benzene); $[\alpha]_D$ = −22.4° (c = 2.0 in benzene)[14]). The step determining the absolute stereochemistry of the initial C−C-bond formation in our cascade resembles the stereodetermining step in the formation of 7. Therefore, we assigned the absolute configuration obtained in our cascades accordingly.

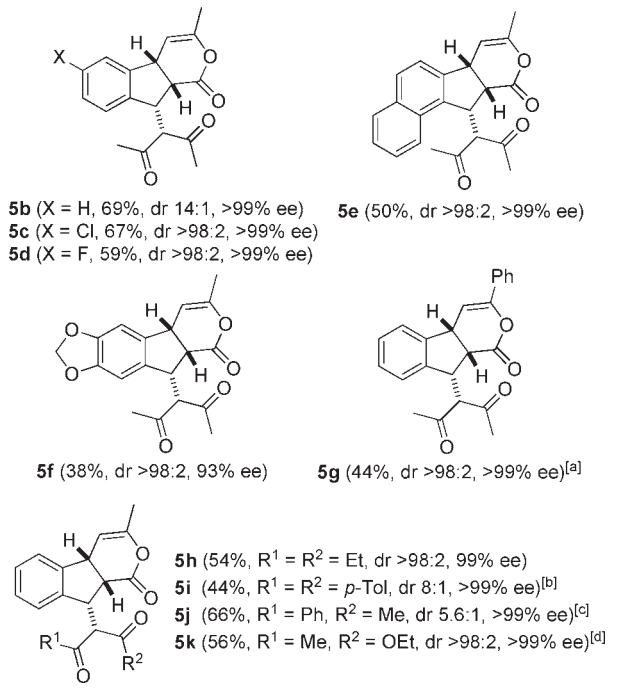
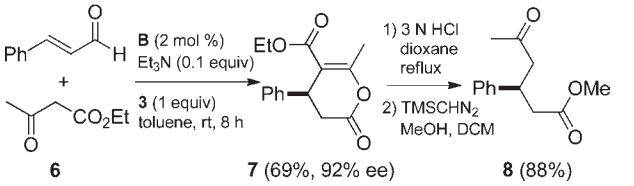


Figure 1. Compounds **5b**−**k** successfully prepared (Conditions: toluene, NEt_3 (1.2 equiv), **B** (5 mol %), 16 h. [a]24 h reaction time. [b]30 h reaction time. [c]*dr* at additional stereocenter = 1.3:1. [d]*dr* at additional stereocenter = 3.6:1).

Scheme 2. Reaction of Cinnamaldehyde with **6** and Subsequent Transformation to Known Ester **8**



We predict that the reaction occurs via the catalytic cycle as depicted in Scheme 3. Reaction of enal **9** with carbene **B′** in the presence of oxidant **3** generates acylazolium ion **10**.[9] Conjugate addition of the likely deprotonated 1,3-dicarbonyl compound to the redox activated Michael acceptor provides **11**. As suggested by Bode, the same intermediate may also be formed via a Claisen-type rearrangement.[11c,d] Enolate **11** can undergo intramolecular 1,4-addition[4b,15] to generate **12** (via **13**), which undergoes intramolecular acylation to eventually afford product **5** and catalyst **B′**.

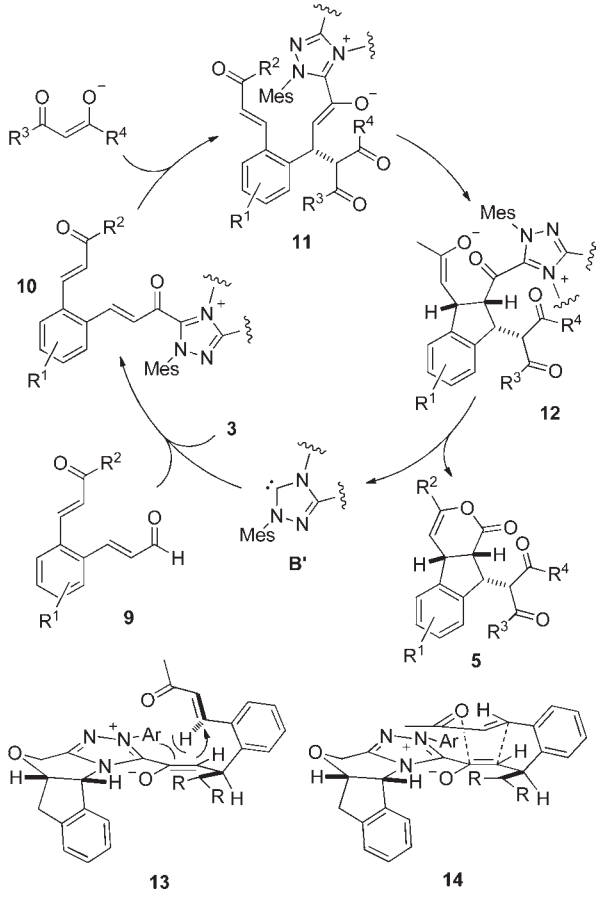
(13) Vora, H. U.; Lathrop, S. P.; Reynolds, N. T.; Kerr, M. S.; deAlaniz, J. R.; Rovis, T. *Org. Synth.* **2010**, *87*, 350.

(14) Sato, M.; Kano, K.; Kitazawa, N.; Hisamichi, H.; Kaneko, C. *Heterocycles* **1990**, *31*, 1229.

(15) Conjugate addition in NHC-catalyzed cascade reactions: Fang, X.; Jiang, K.; Xing, C.; Hao, L.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 1910.

Alternatively, enolate **11** can be transformed via an *endo*-Hetero-Diels–Alder reaction[16] (see **14**) and subsequent carbene fragmentation to product **5**.[17]

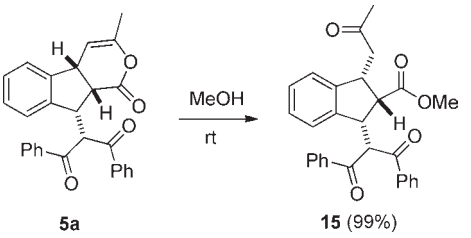
Scheme 3. Suggested Catalytic Cycle



The high *cis*-selectivity for the second C–C-bond formation can be understood by considering model **13**. The H-atom of the Michael acceptor points toward the enolate for steric reasons leading to the observed *cis*-intermediate **12**. If the second bond formation occurs via a Hetero –Diels–Alder reaction, the *endo*-rule (see **14**)[16b] would explain the *cis*-selectivity. The very high enantioselectivities (>99%) achieved for most of the transformations need further comments. We have shown that under optimized conditions, C–C-bond formation in systems that lack the second Michael-acceptor occurs with moderate to very good selectivities (80–93% ee, an example is depicted in Scheme 2). However, the selectivities achieved for the cascades far exceed those ee's. It is therefore likely that the diastereoisomer of **13** (not shown, diastereomeric at the newly formed stereogenic center) does not efficiently further react (mismatched case) to *trans*,*cis*-**5**. In fact, we never identified that particular isomer in our studies. The nonproductive isomer of **13** might undergo back reaction to **10** or might further react to a product different from **5**. By doing so, the "stereochemical error" occurring in the first C–C-bond formation is corrected in the follow up reaction. Increase of initial selectivity by a subsequent second stereoselective reaction that funnels the "wrong" isomer into a product which is not an enantiomer of the targeted compound is well established in asymmetric synthesis.[18]

Finally, we converted the cascade product **5a** to the corresponding indane derivative by methanolysis under very mild conditions (stirring in MeOH at rt) to provide 1,2,3-trisubstituted indane **15** in a quantitative yield (Scheme 4).

Scheme 4. Stereospecific Methanolysis of **5a**



In conclusion, we presented a new method for the highly enantioselective synthesis of substituted indane derivatives. The method uses oxidative carbene catalysis. Starting materials are readily prepared and products of the cascade reaction are easily transformed to the corresponding 1,2,3-trisubstituted indane derivatives. Such indanes are privileged substructures in medicinal chemistry.

Acknowledgment. We thank the DFG and the NRW Graduate School of Chemistry for funding our work. We dedicate this paper to Prof. Dieter Enders on the occasion of his 65th birthday.

Supporting Information Available. Experimental details, characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) (a) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088. (b) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418. See also:(c) Fang, X.; Chen, X.; Chi, Y. R. *Org. Lett.* **2011**10.1021/ol201917u.

(17) A third mechanistic option suggested by a referee: Reaction might go via a pathway involving initial ring closure in **13** by the diketone moiety (as in refs 9,10) followed by Michael reaction and ring-closing/ring-opening to give **5**.

(18) Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*; University Science Books: Sausalito, 2009; p 563.