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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201802420

Link to VoR: http://dx.doi.org/10.1002/chem.201802420

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Highly Enantioselective Kinetic Resolution of Michael Adducts through *N*-Heterocyclic Carbene Catalysis: An Efficient Asymmetric Route to Cyclohexenes

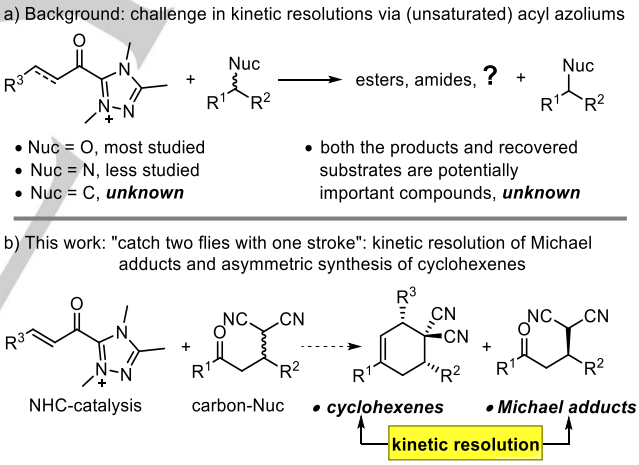
Xiang-Yu Chen+, Sun Li+, Qiang Liu+, Mukesh Kumar, Anssi Peuronen, Kari Rissanen, and Dieter Enders*

Dedicated to Professor Elias James Corey on the occasion of his 90th birthday

Abstract: A highly efficient strategy for the kinetic resolution of Michael adducts was realized using a chiral *N*-heterocyclic carbene catalyst. The kinetic resolution provides a new convenient route to single diastereomers of cyclohexenes and Michael adducts in good yields with high enantiomeric excesses (up to 99% ee with a selectivity factor of up to 458). This "catch two flies with one stroke" concept allows the synthesis of these two synthetically valuable compound classes at the same time by a single transformation.

The value of cyclohexenes lies in their utility as building blocks for a wide variety of biologically active molecules and natural products.[1] Existing synthetic means to access them rely heavily on the Diels–Alder reactions,[2] which is the method of choice to prepare multisubstituted cyclohexenes. There have only been a few alternative asymmetric routes to multisubstituted cyclohexenes including organocatalytic cascade reactions[3] and [4+2] annulations.[4] However, these strategies are not always appropriate for the construction of an envisaged multisubstituted cyclohexene product. Thus, the development of new asymmetric approaches allowing flexible and various substitution patterns remains of great importance and highly desirable.

The kinetic resolution is a reliable and powerful method for the preparation of a wide range of enantioenriched compounds,[5] which serves as an alternative and complementary approach to asymmetric synthesis, even on large scale. Despite the synthetic utility of multisubstituted cyclohexenes, their production by kinetic resolution remains an elusive task. Additionally, the obtained mixture of the product and recovered starting material is a possible demerit to this protocol. However, if both of these compounds are potentially valuable building blocks and obtained in high enantiopurity, such as Michael adducts, this approach would become more attractive. Interestingly, the catalytic kinetic resolution of Michael adducts is surprisingly underdeveloped and there is no efficient method to achieve this transformation. We envisioned that these issues could be accomplished by *N*-heterocyclic carbene (NHC) catalysis. NHCs hold a prominent position among versatile organocatalysts for asymmetric C-C bond formations.[6] Suzuki, Rovis, Maruoka, Scheidt and Studer carried out early studies on the kinetic resolution of alcohols by using NHC catalysis.[7] Very recently, significant progress has been achieved in NHC-catalyzed kinetic resolution of alcohols and amino compounds through (α,β-unsaturated) acyl azolium intermediates by the research groups of Zhao,[8] Yamada,[9] Bolm[10] and Bode[11] (Scheme 1a). The kinetic resolution of oxaziridines and azomethine imines *via* azolium enolate and dienolate intermediates have also been developed by Ye[12] and Chi,[13] respectively. These developments greatly extended the potential of NHC catalysis. Inspired by the synthetic importance of the cyclohexenes and Michael adducts, we herein disclose an NHC-catalyzed enantioselective kinetic resolution of racemic Michael adducts. The protocol allows the preparation of these two highly enantiomerically enriched products by a single transformation (Scheme 1b).



Scheme 1. Motivation and synthetic strategy.

To validate the feasibility of the proposed process, the model reaction of the Michael adduct **1a**[14] and the α-bromoenal **2a** was investigated under NHC catalysis (Table 1). It was found that in the presence of **A** as the pre-catalyst and CsOAc as the base, the reaction proceeded smoothly and afforded the desired product **3a** as a single diastereomer with 97% ee at 37% conversion, albeit with only moderate ee (56%) of the recovered starting material **1a**. A selectivity factor (*s*) of 66 was obtained (entry 1). Encouraged by this promising result, a variety of bases were then screened. It should be noted that the ee of product **3a** was always excellent with different bases, while the ee of the recovered **1a** varied (entries 2-5). Gratifyingly, the employment of NEt_3 as the base significantly improved the ee of the recovered **1a** and gave the best conversion of 52% as well as a high *s* factor of 24 (entry 6). Further improvement was achieved when 4 Å molecular sieves were used as the additive (entry 7). Notably, the gram-scale reaction proceeded smoothly under the standard conditions (entry 8).

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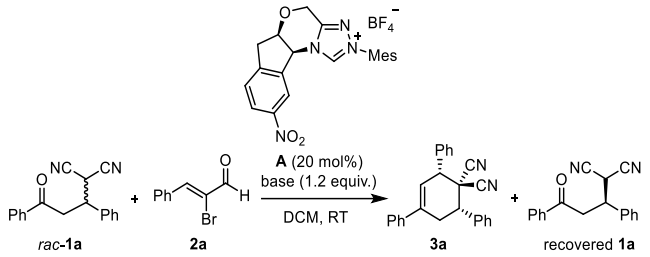
Table 1. Optimization of reaction conditions.



Entry	Base	ee$_{3a}$ [%][a]	ee$_{1a}$ [%][a]	Conv. [%][b]	*s*[b]
1	CsOAc	97	56	37	116
2	NaOAc	97	79	45	159
3	TMEDA	91	23	20	26
4	DABCO	98	28	22	130
5	DBU	97	66	40	130
6	NEt_3	92	99	52	126
7[c]	NEt_3	95	99	51	206
8[d]	NEt_3	97	98	50	304
9[e]	NEt_3	--	--	--	--

[a] The ee was determined by chiral HPLC analysis of the purified products on a chiral stationary phase. [b] Conversions and *s* factor values were calculated by the methods of Kagan: Conv. = ee$_1$/(ee$_1$+ee$_3$), *s* = ln[(1-Conv.)(1-ee$_1$)]/ln[(1-Conv.)(1+ee$_1$)].[15] [c] 4Å MS were added. [d] The reaction was performed on a 4 mmol scale. [e] The reaction of *R*-**1a** with **2a** gave only a trace amount of **3a** and the *R*-**1a** was recovered in 99% yield.

With the optimized conditions in hand, the scope of the kinetic resolution of the Michael adducts with α-bromoenals was studied (Table 2). A series of 2-(3-oxo-1,3-diarylpropyl)malononitriles **1** reacted smoothly. The electronic properties of the substituents at the aromatic ring R^2 had limited effect on the yields and enantioselectivities. The corresponding cyclohexenes **3a**-**f** were obtained with good enantioselectivities of 87-97% ee. The 2-(3-oxo-1,3-diarylpropyl)malononitriles **1a**-**f** were then recovered with excellent enantiopurities, which corresponded to *s* factors of 75-348 (entries 1-6). Substituents at the *meta* or *ortho*-position (3-MeO, 3-Cl and 2-Cl) **1g**-**i** were also well tolerated (entries 7-9). The reaction of more challenging *ortho*, *para*-disubstituted (2,4-Cl_2) substrate also worked well under the optimized reaction conditions giving the corresponding product **3j** in good yield and the highest *s* factor of 458 (entry 10). The reaction of a substrate with a 2-thienyl group showed good selectivity and the cycohexene **3k** was obtained in 90% ee and 41% yield, while **1k** was recovered in 99% ee and 57% yield (*s* = 99; entry 11). The reaction of more electron-donating substrate **1l** reacted as well to give the *s* factor of 111 (entry 12). The R^1 substituents can also be broadly varied including electron-withdrawing aryl, electron-donating aryl and heteroaryl groups. The desired cyclohexenes **3m**-**r** were obtained with good to high enantioselectivities (87-95% ee). Unreacted **1m**−**r** were recovered in the yields of 42-51% with 84-99% ee and with *s* factors ranging from 51 to 111 (entries 13-18). Furthermore, investigations into the effect of substituents at both aromatic rings R^1 and R^2 revealed that the reactions were efficient, affording the desired products **3s**-**v** with good selectivities (89-93% ee, *s* = 90-145; entries 19-22). Notably, all these starting materials were recovered in 99% ee when the conversion was slightly above 50%. For example, (*S*)-**1s** was recovered in 99% ee at 51% conversion (entry 19). We next attempted the reaction with various α-bromoenals. The groups R^3 on α-bromoenals, such as 4-methylphenyl, 4-fluorophenyl, 4-phenylphenyl, 3-chlorophenyl and 2-furyl groups, were well-tolerated giving the corresponding cyclohexenes **3w-a'** with good selectivities (90-98% ee, *s* = 47-170; entries 23-27). Additionally, the Michael adduct of nitromethane to chalcone **1w** was also tolerable with a synthetically useful selectivity factor of 30 (entry 28). Unfortunately, β-alkyl substituted Michael adducts and α-bromoenals as well as dimethyl- and diethylmalonate gave only a trace amount of the products under different reaction conditions.[16]

The absolute configuration of the cyclohexene **3a** was determined by the X-ray structure analysis[17] and the configurations of all other products were assigned accordingly.

A plausible catalytic cycle is depicted in Figure 1. The addition of the NHC catalyst to the α-bromoenal **2a** leads to the formation of the Breslow intermediate **I**, which tautomerizes to the intermediate **II**. The α,β-unsaturated acyl azolium intermediate **III** is then formed *via* bromide elimination.[18] The Michael addition of the Michael adduct *rac*-**1a** to the α,β-unsaturated acyl azolium **III** from the opposite side of the catalyst chiral backbone forms the C−C bond[19] and generates the azolium enolate **IV**.[20] Subsequently, an intramolecular aldol lactonization leads to the unstable β-lactone **V** and regenerates the NHC catalyst. A final decarboxylation [21] affords the desired cyclohexene **3a**.

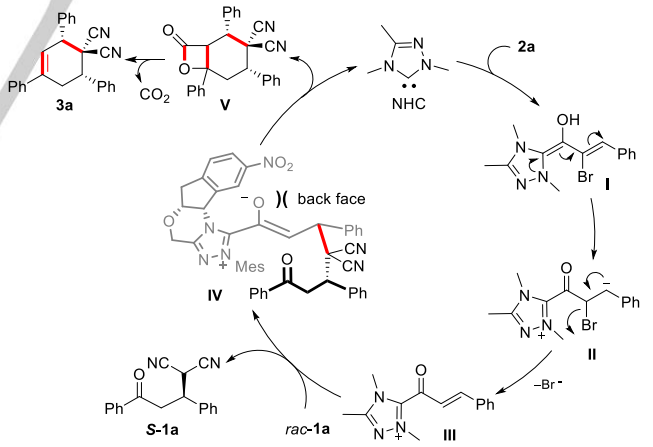
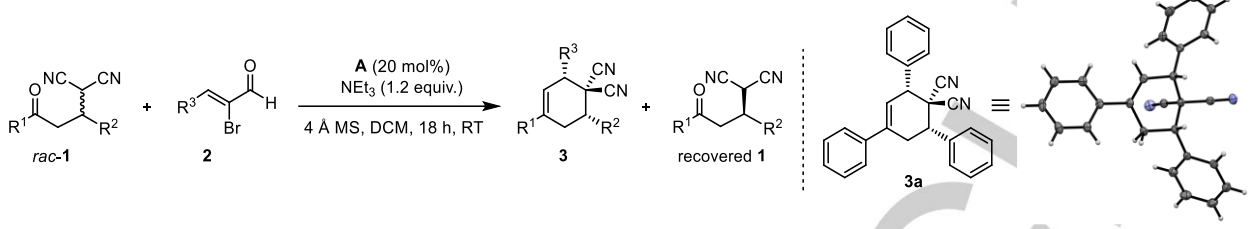


Figure 1. Plausible catalytic cycle.

To demonstrate the synthetic usefulness of the present catalytic strategy, an one-pot protocol for the asymmetric synthesis of multisubstituted cyclohexenes was developed. Good yields for a five-step transformation (22–38%) were observed with excellent stereoselectivities (Table 3).

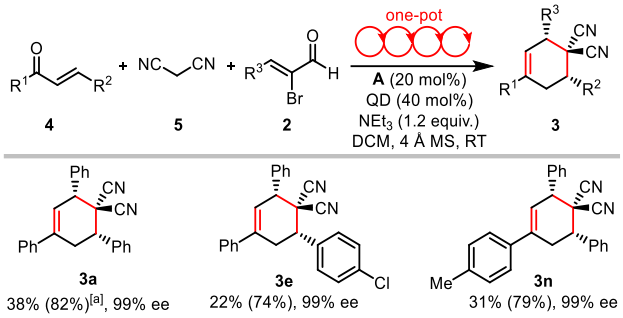
Table 2. Substrate scope for the kinetic resolution of Michael adducts with α-bromoenals.



Entry	R^1	R^2	R^3	Yield of **3** [%][a]	ee of **3** [%][b]	Yield of **1** [%][a]	ee of **1** [%][b]	Conv.[%]	*s*
1	Ph	Ph	Ph	54 (**3a**)	95	44 (**1a**)	99	51	206
2	Ph	4-$MeOC_6H_4$	Ph	51 (**3b**)	87	48 (**1b**)	99	53	75
3	Ph	4-MeC_6H_4	Ph	49 (**3c**)	93	51 (**1c**)	99	52	145
4	Ph	4-FC_6H_4	Ph	51 (**3d**)	90	44 (**1d**)	99	52	99
5	Ph	4-ClC_6H_4	Ph	51 (**3e**)	92	44 (**1e**)	97	51	101
6	Ph	4-BrC_6H_4	Ph	56 (**3f**)	97	43 (**1f**)	99	51	348
7	Ph	3-$MeOC_6H_4$	Ph	55 (**3g**)	95	42 (**1g**)	99	51	205
8	Ph	3-ClC_6H_4	Ph	43 (**3h**)	88	55 (**1h**)	97	52	65
9	Ph	2-ClC_6H_4	Ph	46 (**3i**)	97	52 (**1i**)	99	51	348
10	Ph	2,4-$Cl_2C_6H_3$	Ph	50 (**3j**)	98	47 (**1j**)	98	50	458
11	Ph	2-thienyl	Ph	41 (**3k**)	90	57 (**1k**)	99	52	99
12	Ph	3,4-$O_2CH_2C_6H_3$	Ph	40 (**3l**)	91	59 (**1l**)	99	52	111
13	4-$MeOC_6H_4$	Ph	Ph	45 (**3m**)	95	51 (**1m**)	84	47	104
14	4-MeC_6H_4	Ph	Ph	55 (**3n**)	91	44 (**1n**)	99	52	111
15	4-FC_6H_4	Ph	Ph	53 (**3o**)	87	46 (**1o**)	99	53	75
16	4-ClC_6H_4	Ph	Ph	56 (**3p**)	87	42 (**1p**)	99	53	75
17	3-ClC_6H_4	Ph	Ph	49 (**3q**)	88	50 (**1q**)	92	51	51
18	2-thienyl	Ph	Ph	53 (**3r**)	90	-- (**1r**)[c]	--	--	--
19	4-MeC_6H_4	4-MeC_6H_4	Ph	45 (**3s**)	93	52 (**1s**)	99	51	145
20	4-MeC_6H_4	4-ClC_6H_4	Ph	38 (**3t**)	89	54 (**1t**)	99	52	90
21	4-ClC_6H_4	4-MeC_6H_4	Ph	38 (**3u**)	90	61 (**1u**)	99	52	99
22	4-FC_6H_4	4-ClC_6H_4	Ph	38 (**3v**)	92	49 (**1v**)	99	52	126
23	Ph	Ph	4-MeC_6H_4	50 (**3w**)	91	45 (**1a**)	99	52	111
24	Ph	Ph	4-FC_6H_4	42 (**3x**)	94	57 (**1a**)	99	51	170
25	Ph	Ph	4-PhC_6H_4	30 (**3y**)	98	49 (**1a**)	41	30	148
26	Ph	Ph	3-ClC_6H_4	44 (**3z**)	90	55 (**1a**)	81	47	47
27	Ph	Ph	2-furyl	52 (**3a'**)	89	47 (**1a**)	99	53	90
28[d]	Ph	Ph	Ph	20 (**3b'**)	90	57 (**1w**)	46	34	30

[a] Yields of isolated products. [b] The ee was determined by chiral HPLC analysis of the purified product on a chiral stationary phase. [c] The unreacted **1r** was unstable under the current conditions and unisolable. [d] The Michael adduct of nitromethane to chalcone was used as substrate (*rac*-**1w**).

Table 3. One-pot Michael/Michael/aldol/lactonization/decarboxylation reaction.



[a] Value within parentheses is the average yield per step. QD = quinidine.

In conclusion, we have developed a highly efficient and practical strategy for the kinetic resolution of racemic Michael adducts. This strategy allows not only the recovery of the Michael adducts with high enantiomeric excess, but also the asymmetric synthesis of multisubstituted cyclohexenes in good yields and very high stereoselectivity in a single transformation. The scalable procedure can be carried out under one-pot conditions and constitutes a valuable alternative to existing asymmetric protocols.

Acknowledgements ((optional))

Support from the European Research Council (ERC Advanced Grant 320493 “DOMINOCAT”) is gratefully acknowledged.

Keywords: *N*-heterocyclic carbenes • kinetic resolution • cyclohexenes • Michael adducts • asymmetric synthesis

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10.1002/chem.201802420

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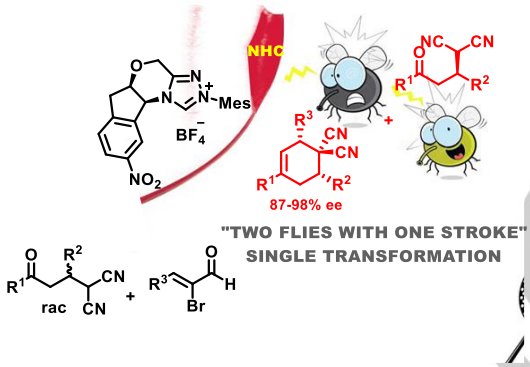

*Xiang-Yu Chen, Sun Li, Qiang Liu, Mukesh Kumar, Anssi Peuronen, Kari Rissanen, and Dieter Enders**

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Highly Enantioselective Kinetic Resolution of Michael Adducts through *N*-Heterocyclic Carbene Catalysis: An Efficient Asymmetric Route to Cyclohexenes