Asymmetric Synthesis

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An Enantioselective Inverse-Electron-Demand Imino Diels–Alder Reaction**

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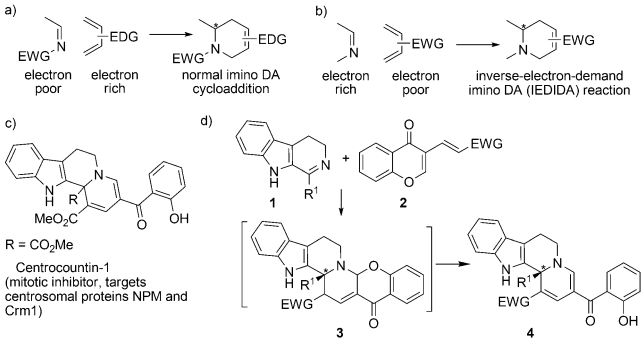
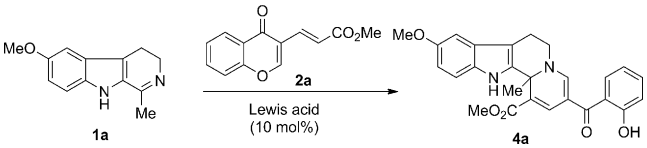
Abstract: *The imino Diels–Alder reaction is an efficient method for the synthesis of aza-heterocycles. While different stereo- and enantioselective inverse-electron-demand imino Diels–Alder (IEDIDA) reactions have been reported before, IEDIDA reactions including electron-deficient dienes are unprecedented. The first enantioselective IEDIDA reaction between electron-poor chromone dienes and cyclic imines, catalyzed by zinc/binol complexes is described. The novel reaction provides a facile entry to a natural product inspired collection of ring-fused quinolizines including a potent modulator of mitosis.*

The imino Diels–Alder reaction is among the most powerful methods for the synthesis of chiral nitrogen heterocycles.[1] In this cycloaddition, typically electron-poor or electron-neutral imines[2] and electron-rich dienes are employed in the presence of Lewis acid catalysts (Scheme 1 a).[3] However, cycloaddition reactions between electron-rich imines and electron-deficient dienes, that is the inverse-electron-demand imino Diels–Alder (IEDIDA) reactions (Scheme 1 b) have not been reported.[4] Herein we describe the first example of an IEDIDA reaction, that is, the cycloaddition between the imines **1** and **6**–**9** (Tables 1–4) and the dienes **2**. The reaction proceeds with high enantioselectivity in the presence of a chiral zinc Lewis acid catalyst. The centrocountins (Scheme 1 c) are novel mitosis modulators, accessible by means of a one-pot, 12-step cascade reaction sequence.[5] To extensively explore their bioactivity, we envisaged an alternative efficient and enantioselective synthesis by a Lewis acid catalyzed IEDIDA reaction between electron-rich imines (**1**; Scheme 1, Tables 1–3) and chromone-derived dienes (**2**) through the intermediary formation of the cycloadducts **3** (Scheme 1 d).



Scheme 1. Strategy for heterocycle synthesis by means of imino Diels–Alder reactions. a and b) Combination of electron-rich and electron-poor dienes and dienophiles in IEDIDA reactions. c) Structure of centrocountin-1. d) IEDIDA reaction between various imines and electron-deficient chromone dienes. EDG = electron-donating group, EWG = electron-withdrawing group.

Table 1: IEDIDA reaction between imine **1a** and diene **2a**.



Entry	Lewis Acid	Solvent	T [°C]	t [h]	Yield [%][a]
1	none	DMSO	80	48	61
2	$AlCl_3$	CH_2Cl_2	RT	12	–
3	$ZnCl_2$	THF	60	12	–
4	$ZnCl_2$	DMF	80	12	–
5	$ZnCl_2$	CH_2Cl_2	RT	12	69
6	$ZnCl_2$	toluene	80	12	83
7	$ZnCl_2$	DMSO	80	1	94
8	$ZnCl_2$	DMSO	RT	12	85

[a] Yields of isolated products. DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, THF = tetrahydrofuran.

Indeed, treatment of the imine **1a** with the diene **2a** in DMSO at 80 °C for 48 hours induced the desired IEDIDA reaction and led to the formation of the desired indoloquinolizine **4a** in 61 % yield (Table 1, entry 1). Variation of solvent and temperature, and exploration of different Lewis acids revealed that the cycloaddition proceeds best in the presence of $ZnCl_2$ in toluene or DMSO at 80 °C (Table 1, entries 6–8).

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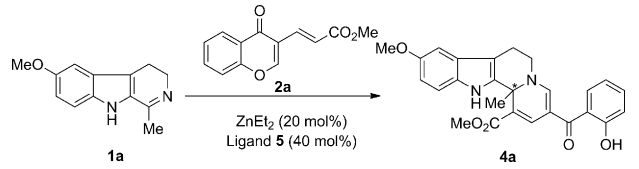
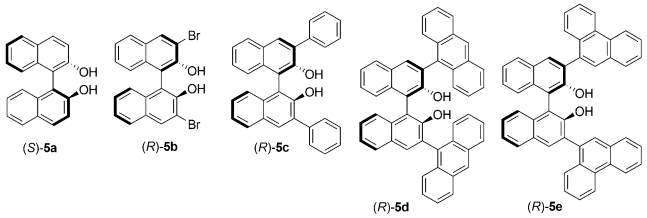
Table 2: Enantioselective IEDIDA reaction of **1a** and **2a**.



Entry	Ligand	Solvent	T[°C]	t [h]	Yield [%][a]	*ee* [%][b]
1	(*S*)-**5a**	toluene	RT	24	83	24
2	(*S*)-**5a**	toluene	0	24	72	39
3	(*S*)-**5a**	toluene	−15	24	69	61
4	(*S*)-**5a**	toluene	−78	24	66	88
5	(*S*)-**5a**	CH_2Cl_2	−78	24	71	47
6	(*S*)-**5a**	methanol	−78	24	83	14
7	(*S*)-**5a**	THF	−78	24	94	68
8	(*R*)-**5a**	toluene	−78	24	67	90
9	(*R*)-**5b**	toluene	−78	24	0	–
10	(*R*)-**5c**	toluene	−78	24	70	83
11	(*R*)-**5d**	toluene	−78	24	13	89
12	(*R*)-**5e**	toluene	−78	24	51	93

[a] Yields of isolated products. [b] Determined by HPLC analysis using a chiral stationary phase.



To develop an enantioselective IEDIDA reaction we employed binol ligands[6] and envisioned that tetracoordination of a zinc Lewis acid by the binol ligand, the imine nitrogen atom, and the vinylogous ester incorporated into the chromone-derived diene, would allow for efficient steric discrimination.[7] Treatment of **1a** and **2a** with catalysts formed from 20 mol% of $ZnEt_2$ and 40 mol% of a chiral binol ligand (**5**) in different solvents and at different temperatures revealed that 1) lowering the temperature to −78°C prevented the uncatalyzed non-enantioselective reaction and led to an increase of the *ee* value to 88% (Table 2, entries 1–4), 2) toluene is best among the explored solvents (Table 2, entries 4–7), 3) introduction of sterically demanding substituents into the 3- and 3′-positions of the binol ligand leads to an increase in enantioselectivity. The use of dibromo (*R*)-**5b** led to decomposition of the starting material.

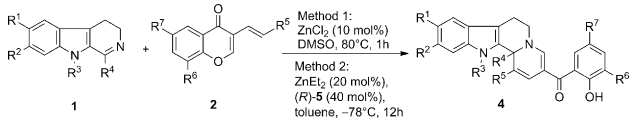
The absolute configuration of the cycloadduct **4a** was determined by comparison of its CD spectrum with the spectrum recorded for the structurally closely related centrocountin-1 (Scheme 1) reported earlier (see the Supporting Information).[5a]

For exploration of the bioactivity of the centrocountins and to explore the scope of the IEDIDA reaction, we investigated different electron-poor dienes (**2**) and electron-rich cyclic heterodienophiles (**1**) for the synthesis of a compound collection. Introduction of substituents onto the chromone ring of the diene consistently yields cycloadducts with high *ee* values (Table 3) and does not markedly influence the reactivity. Thus, both chromenyl acrylates (**2**, $R^5 = CO_2Me$) and chromenyl acrylonitriles (**2**, $R^5 = CN$) reacted smoothly with imines (**1**) to provide the indoloquinolizines **4** in excellent yields (Table 3). Indole-derived imines incorporating a methoxy group yielded the cycloadducts in high yields and with high to very high *ee* values. Imines with a substituent (R^4) at the imine carbon atom yielded the desired indoloquinolizines in very high yields and predominantly with high enantioselectivity (Table 3, entries 1–12). In contrast, in the absence of a substituent at the imine carbon atom ($R^4 = H$) the enantioselectivity was low (Table 3, entries 13–14; for additional examples, see the Supporting information).

Different hetero- and carbocyclic imines (**6–9**) yielded the corresponding cycloadducts **10–13** in good to excellent yields (Table 4). Only for the imine **9** ($n = 2$), which is prone to trimerization,[8] were moderate yields of the cycloadducts **14** recorded. Additionally, selected electron-poor cyclic dienes (see Reference [9]) did not react with the indole derived imines **1** under the developed reaction conditions.[9]

Both (*R*)-**5a** and (*R*)-**5e** yielded the cycloadducts with high *ee* values, and electron-donating and electron-accepting substituents on the chromone ring of the dienes as well as

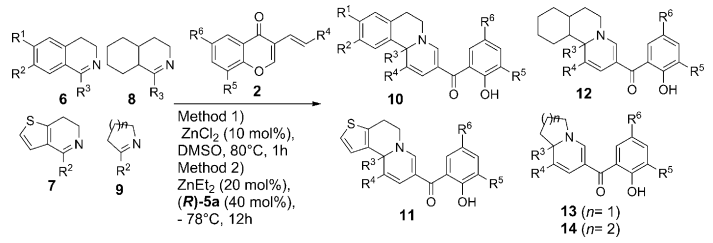
Table 3: Enantioselective synthesis of tetrahydro-indoloquinolizines **4** by means of the IEDIDA reaction.



Entry	4	Ligand	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield [%][a,b]	Yield [%][a,c]	*ee* [%][d]
1	**4a**	(*R*)-**5e**	OMe	H	H	Me	CO_2Me	H	H	91	51	93
2	**4b**	(*R*)-**5e**	OMe	H	H	Me	CN	H	H	85	82	92
3	**4c**	(*R*)-**5e**	H	OMe	H	Me	CO_2Me	H	H	94	81	95
4	**4d**	(*R*)-**5e**	H	OMe	H	Me	CN	H	H	89	79	91
5	**4e**	(*R*)-**5a**	H	OMe	H	Me	CO_2Me	H	Me	94	94	90
6	**4f**	(*R*)-**5a**	H	OMe	H	Me	CO_2Me	H	Cl	97	80	91
7	**4g**	(*R*)-**5a**	H	OMe	H	Me	CO_2Me	Cl	Cl	94	95	71
8	**4h**	(*R*)-**5e**	H	OMe	Me	Me	CO_2Me	H	H	97	91	94
9	**4i**	(*R*)-**5e**	H	OMe	Me	Me	CN	H	H	97	90	89
10	**4j**	(*R*)-**5a**	H	OMe	Me	Me	CO_2Me	H	Me	93	96	91
11	**4k**	(*R*)-**5a**	H	OMe	Me	Me	CN	H	Me	96	79	88
12	**4l**	(*R*)-**5a**	H	OMe	Me	Me	CO_2Me	H	Cl	89	93	89
13	**4m**	(*R*)-**5a**	H	H	H	H	CO_2Me	H	H	71	82	19
14	**4n**	(*R*)-**5a**	H	H	H	H	CN	H	H	97	84	23

[a] Yields of isolated products. [b] Racemic synthesis (Method 1). [c] Enantioselective synthesis (Method 2). [d] Determined by HPLC analysis using a chiral stationary phase.

Table 4: IEDIDA reaction of various cyclic imines **6**–**9** with chromone dienes **2**.



Entry	Prod.	Ligand	R^1	R^2	R^3	R^4	R^5	R^6	Yield [%][a,b]	Yield [%][a,c]	*ee* [%][d]
1	**10a**	(*R*)-**5e**	H	H	Me	CO_2Me	H	H	89	75	93
2	**10b**	(*R*)-**5e**	H	H	Me	CN	H	H	91	79	91
3	**10c**	(*R*)-**5e**	H	H	Et	CO_2Me	H	H	84	54	83
4	**10d**	(*R*)-**5e**	H	H	*i*Pr	CO_2Me	H	H	80	51	69
5	**10e**	(*R*)-**5e**	H	H	Cy	CO_2Me	H	H	79	47	91
6	**10f**	(*R*)-**5a**	OMe	OMe	Cy	CN	H	H	83	41	84
7	**10g**	(*R*)-**5e**	OMe	OMe	Me	CO_2Me	H	Me	92	71	87
8	**10h**	(*R*)-**5a**	OMe	OMe	Me	CN	H	Me	94	84	80
9	**10i**	(*R*)-**5a**	OMe	OMe	Et	CO_2Me	H	Me	81	67	82
10	**10j**	(*R*)-**5a**	OMe	OMe	Me	CO_2Me	Cl	Cl	91	90	88
11	**10k**	(*R*)-**5a**	OMe	OMe	Me	CN	Cl	Cl	97	86	86
12	**10l**	(*R*)-**5a**	OEt	OEt	Me	CO_2Me	H	H	76	71	83
13	**10m**	(*R*)-**5a**	OEt	OEt	Me	CN	H	H	77	80	83
14	**10n**	(*R*)-**5a**	OMe	OMe	Me	CO_2Me	H	Cl	92	86	87
15	**10o**	(*R*)-**5a**	OMe	OMe	Me	CN	H	Cl	96	90	83
16	**10p**	(*R*)-**5a**	H	H	H	CO_2Me	H	H	93	81	27
17	**10q**	(*R*)-**5a**	H	H	H	CN	H	H	96	84	24
18	**11a**	–	–	–	H	CO_2Me	H	H	87	–	
19	**11b**	–	–	–	H	CN	H	H	91	–	
20	**12a**	–	–	–	H	CO_2Me	H	H	95	–	
21	**12b**	–	–	–	H	CN	H	H	97	–	
22	**12c**	–	–	–	H	CO_2Me	H	Cl	77	–	
23	**12d**	–	–	–	H	CN	H	Cl	83	–	
24	**13a**	(*R*)-**5a**	–	–	Me	CO_2Me	H	H	66	62	44
25	**13b**	(*R*)-**5a**	–	–	Me	CN	H	H	68	62	29
26	**14a**	–	–	–	H	CO_2Me	H	H	51	–	
27	**14b**	–	–	–	H	CN	H	H	54	–	

[a] Yields of isolated products. [b] Racemic synthesis (Method 1), [c] Enantioselective synthesis (Method 2). [d] Determined by HPLC analysis using a chiral stationary phase.

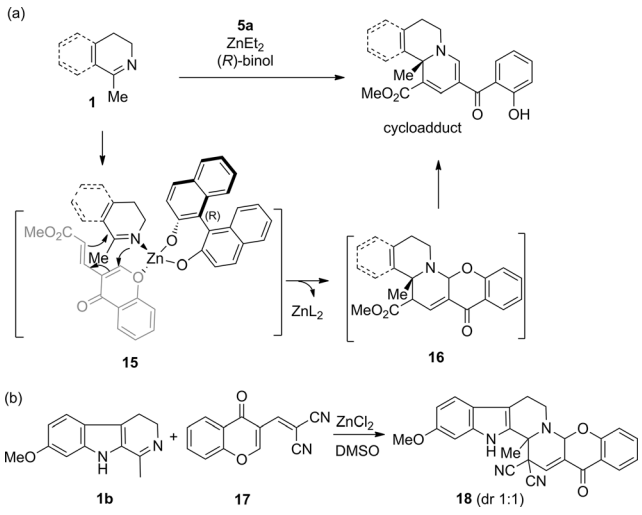
different α-substituents on the imines **6**–**9** were tolerated (Table 4, entries 1–15). In general, unsubstituted dienophiles yielded the corresponding cycloadducts in good to high yields, however, in these cases stereoselectivity was low (Table 4, entries 16–23, 26, and 27). Most of these heterodienophiles were not stable, however, for imine **9** ($n = 1$) the cycloadducts were formed with moderate *ee* values (Table 4, entries 24 and 25).

To rationalize the stereochemical course of the IEDIDA reaction we assume that a preformed zinc/binol complex coordinates the imine nitrogen atom and the vinylogous ester oxygen atom of the diene (Scheme 2a). In the ensuing complex **15**, one naphthalene ring would be oriented orthogonal to the plane of the heterodienophile and thus shields the *Si* face of the imine. Thereby the attack of the diene is directed to the *Re* face of the imines. α-Alkyl groups on the imines will avoid the steric bias of the naphthalene ring, thus leading to high stereoselectivity. Consequently, for nonsubstituted imines enantioselectivity is lower.

Rapid reorganization of the hexacyclic intermediate (**3**; Scheme 1) into quinolizines (**4**, **10**–**14**) led us to employ the chromone diene **17** to identifiy the primary cycloadduct **18**. We assumed that in the absence of an α-acidic proton in **18**, chromone ring-opening might be prevented. Indeed, the reaction between **1b** and **17** (Scheme 2b) provided the hexacyclic indoloquinolizine **18** in 64% yield. However, **18** is sensitive to Brønsted acids which facilitates retro-IEDIDA reaction.

For a phenotypic cell based investigation[10] into whether the new compounds share the ability of the centrocountins to impair centrosome integrity,[5a] which leads to defects in chromosome congression and to arrest of cells in metaphase of mitosis, human cervical carcinoma HeLa cells were treated with the compounds for 24 hours. Cells were then stained for DNA and the mitotic marker phospho-histone H3 to determine the proportion of cells arrested in mitosis. High-content analysis was employed to calculate the percentage of mitotic cells. Several compounds led to accumulation of mitotic cells and the compound **10p** was identified as most potent (Figure 1).

Only the *S*-configured cycloadduct arrested the cells in mitosis whereas the *R* enantiomer was inactive (see Figure 1a). Treatment of HeLa cells for 48 hours with the racemate of **10p** and the enantiomers, and determination of cell viability by means of the WST-1 reagent revealed that (±)**10p** reduced the viability of HeLa cells with a half-maximal inhibitory concentration (IC_{50}) of (9.7 ± 1.1) μM, whereas (*S*)-**10p** more potently inhibited cell proliferation with an IC_{50} of (4.7 ± 0.5) μM (Figure 1b). The *R* enantiomer again proved to be inactive. Notably, (±)**10p** and (*S*)-**10p** were more potent than the guiding centrocountin-1 [IC_{50} (17.2 ± 2.4) μM]. Accumulation of mitotic cells upon treatment with **10p** followed by cell death was independ-



Scheme 2. a) Rationale for stereoselection in the asymmetric imino Diels–Alder reaction. b) Synthesis of the hexacyclic cycloadduct **18**.

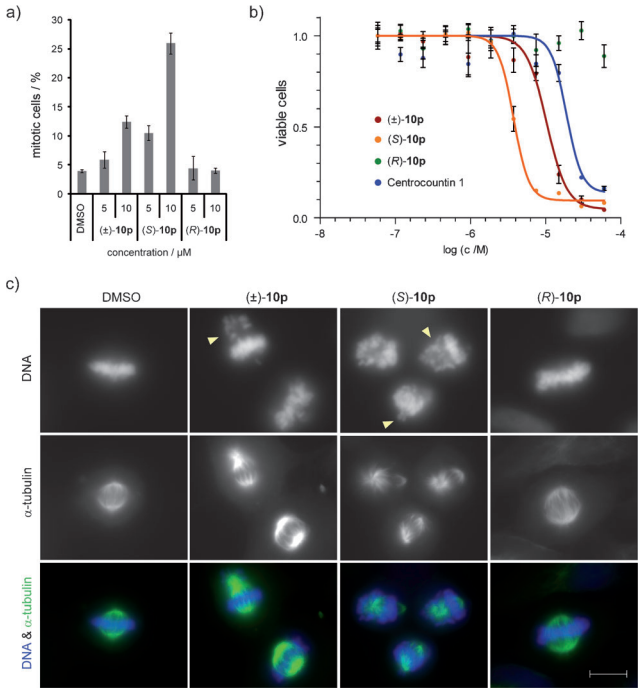


Figure 1. The compound **10p** induces chromosome congression defects and mitotic arrest in HeLa cells. a) HeLa cells were treated with compounds for 24 hours prior to staining with an anti-phospho-histone H3 antibody and 4′,6-diamidino-2-phenylindole (DAPI) to detect the mitotic marker phospho-histone H3 and DNA, respectively. High-content analysis was performed to determine the percentage of mitotic cells in the cell populations. Data are shown as mean values with standard deviations. b) Influence of (±)-**10p** , (*S*)- and (*R*)-**10p** on the viability of HeLa cells. Cells were treated with the compounds for 48 h prior to determination of cell viability using the WST-1 proliferation reagent. Data were normalized to DMSO and represent mean values with standard deviations. c) (±)-**10p** and (*S*)-**10p** cause chromosome congression defects. HeLa cells were treated with compounds at a concentration of 10 μM for 24 h prior to staining with anti-α-tubulin antibody coupled to FITC (green) and DAPI (blue) to visualize tubulin and DNA respectively. Arrows indicate misaligned chromosomes during metaphase. Scale bar: 10 μm.

ently confirmed by means of live-cell imaging (see the Supporting movies 1 and 2). Mitotic HeLa cells accumulated after 6 hours of treatment with 7.5 μM (±)**10p**. Cell death was observed as early as 24 hours post compound addition. Immunostaining of DNA and tubulin revealed misaligned chromosomes during metaphase induced by (±)**10p** and (*S*)-**10p** (Figure 1c). In contrast, cells that were treated with (*R*)-**10p** underwent proper mitosis.

In conclusion, we have developed a catalytic and asymmetric inverse-electron-demand imino Diels–Alder reaction between various cyclic imines and chromone-derived dienes. To the best of our knowledge, this is the first report of an asymmetric IEDIDA reaction involving electron-deficient dienes and electron-rich imines. Use of the asymmetric IEDIDA reaction as the key transformation in the synthesis of quinolizines yielded a centrocountin analogue with increased potency compared to that of centrocountin-1.

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[1] a) H. Waldmann, *Synthesis* **1994**, 535–551; b) G. R. Heintzelman, I. R. Meigh, Y. R. Mahajan, S. M. Weinreb, *Org. React.* **2005**, *65*, 141; c) G. Masson, C. Lalli, M. Benohoud, G. Dagousset, *Chem. Soc. Rev.* **2013**, *42*, 902–923; d) V. V. Kouznetsov, *Tetrahedron* **2009**, *65*, 2721–2750.

[2] a) K. Ishihara, M. Miyata, K. Hattori, T. Tada, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 10520–10524; b) K. Hattori, H. Yamamoto, *J. Org. Chem.* **1992**, *57*, 3264–3265; c) K. Hattori, H. Yamamoto, *Tetrahedron* **1993**, *49*, 1749–1760; d) J. P. Cros, Y. Perez-Fuertes, M. J. Thatcher, S. Arimori, S. D. Bull, T. D. James, *Tetrahedron: Asymmetry* **2003**, *14*, 1965–1968.

[3] a) H. Ishitani, S. Komiyama, S. Kobayashi, *Angew. Chem.* **1998**, *110*, 3369–3372; *Angew. Chem. Int. Ed.* **1998**, *37*, 3186–3188; b) E. Jnoff, L. Ghosez, *J. Am. Chem. Soc.* **1999**, *121*, 2617–2618; c) T. Akiyama, Y. Tamura, J. Itoh, H. Morita, K. Fuchibe, *Synlett* **2006**, 141–143; d) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2006**, *118*, 4914–4916; *Angew. Chem. Int. Ed.* **2006**, *45*, 4796–4798; e) P. R. Girling, T. Kiyoi, A. Whiting, *Org. Biomol. Chem.* **2011**, *9*, 3105–3121.

[4] a) P. Buonora, J. C. Olsen, T. Oh, *Tetrahedron* **2001**, *57*, 6099–6138; b) X. X. Jiang, R. Wang, *Chem. Rev.* **2013**, *113*, 5515–5546.

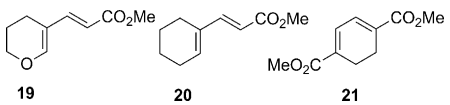
[5] a) H. Dückert, V. Pries, V. Khedkar, S. Menninger, H. Bruss, A. W. Bird, Z. Maliga, A. Brockmeyer, P. Janning, A. Hyman, S. Grimme, M. Schurmann, H. Preut, K. Hubel, S. Ziegler, K. Kumar, H. Waldmann, *Nat. Chem. Biol.* **2012**, *8*, 179–184; b) V. Eschenbrenner-Lux, H. Dückert, V. Khedkar, H. Bruss, H. Waldmann, K. Kumar, *Chem. Eur. J.* **2013**, *19*, 2294–2304.

[6] a) H. Ishitani, S. Kobayashi, *Tetrahedron Lett.* **1996**, *37*, 7357–7360; b) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. P. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598–4599; c) S. Kobayashi, K. Kusakabe, S. Komiyama, H. Ishitani, *J. Org. Chem.* **1999**, *64*, 4220–4221.

[7] S. Guillarme, A. Whiting, *Synlett* **2004**, 711–713.

[8] A. Rouchaud, J. C. Braekman, *Eur. J. Org. Chem.* **2009**, 2666–2674.

[9] Electron-poor cyclic dienes (**19**–**21**) were investigated in the IEDIDA reaction with various indole-derived imines (**1**) but did not give the desired products.



19 **20** **21**

[10] a) A. E. Carpenter, *Nat. Chem. Biol.* **2007**, *3*, 461–465; b) Y. Feng, T. J. Mitchison, A. Bender, D. W. Young, J. A. Tallarico, *Nat. Rev. Drug Discovery* **2009**, *8*, 567–578.

