[3+2] Cycloaddition

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Enantiodivergent Combination of Natural Product Scaffolds Enabled by Catalytic Enantioselective Cycloaddition

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Abstract: *An efficient strategy has been established for the enantiodivergent synthesis of natural product inspired compounds embodying both tropane and pyrrolidine natural product fragments. This strategy includes the enantioselective kinetic resolution of racemic tropanes by means of a copper(I)-catalyzed [3+2] cycloaddition and allows the preparation of two enantiopure products in a one-pot reaction in high yield and with high diastereo- and enantioselectivity by using one chiral catalyst.*

Bioactive natural products define biologically prevalidated scaffold structures because they encode the areas of chemical space explored by nature during evolution.[1] Since fragment-based design principles allow large fractions of biologically relevant chemical space to be covered efficiently with a limited number of small molecules,[2] it would be highly desirable to unite them with hypothesis-generating approaches that take inspiration form natural product structures, in particular biology-oriented synthesis (BIOS).[1,2] We have recently described the cheminformatic dissection of natural products to arrive at fragments that represent natural product structures and their properties, in particular stereogenic character.[3] Combinations of such natural product fragments and scaffolds may give access to novel classes of bioactive compounds since they will inherit natural product structure and properties.[4] The corresponding syntheses need to address the fact that the bioactivity of natural products is often tied to their absolute configuration, which can hardly be predicted for the novel scaffolds derived from the combination of chiral fragments. The development of enantiodivergent syntheses that provide efficient access to both possible enantiomers would provide a powerful solution to this problem.

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The synthesis of both enantiomers from a single chiral intermediate, usually by multistep transformations, has been documented[5] and, recently, a few more streamlined solutions to this problem were found for the synthesis of compounds with one stereocenter.[6] However, efficient methods for the enantiodivergent synthesis of complex molecular architectures with multiple stereocenters are rare.[6f] Here we report a catalytic enantiodivergent synthesis of enantiopure complex natural product inspired compounds which embody different natural product fragments and scaffolds and carry multiple stereocenters. Importantly, both enantiomers can be accessed rapidly and efficiently using just one chiral ligand with a defined absolute configuration.

The tropane scaffold, that is, 8-azabicyclo[3.2.1]octane, defines the core structure of more than 600 alkaloids with multiple bioactivities (Figure 1),[7] and tropanes have been

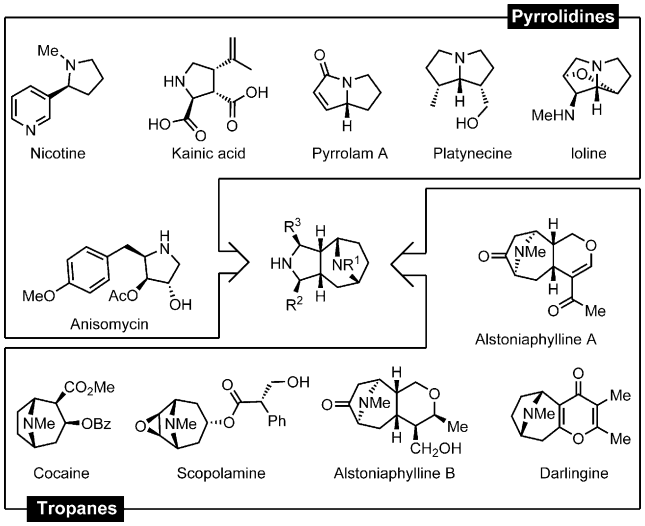
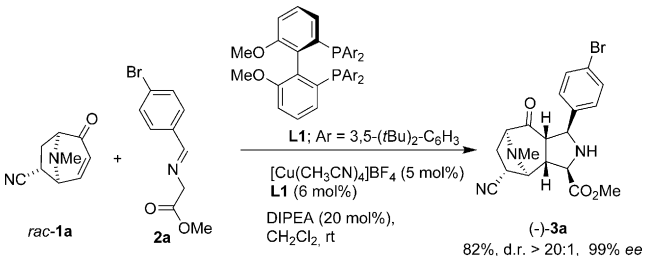


Figure 1. Design of natural product hybrid structures derived from the tropane and pyrrolidine alkaloids. Bz = benzoyl.

subjected to numerous synthetic and biological studies.[8] However, most of the synthesis methods yield racemic compounds, and general methods for the asymmetric catalytic synthesis of functionalized tropanes are in high demand.[9] The 1,3-dipolar cycloaddition of azomethine ylides[10–12] with different olefins gives efficient access to pyrrolidines, which define the characteristic fragment core structure of numerous alkaloids.[7c,13] We envisioned that the combination of this cycloaddition with racemic tropanes (readily accessible by means of a [5+2] cycloaddition of 3-oxidopyrylium

betaines[14,15]) with alkenes could provide a powerful approach to complex polycyclic natural product inspired architectures incorporating both the tropane and pyrrolidine fragment structures.

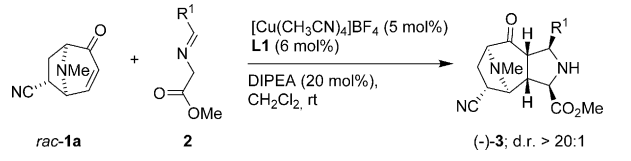
Initially we investigated the reaction conditions for the enantioselective 1,3-dipolar cycloaddition of *N*-4-bromobenzylideneglycine methyl ester (**2a**, 1.0 equiv) with racemic tropane *rac*-**1a** (2.0 equiv; Scheme 1). Variation of different



Scheme 1. Enantioselective 1,3-dipolar cycloaddition of azomethine ylide **2a** with tropane *rac*-**1a**. DIPEA = diisopropylethylamine.

reaction parameters, in particular catalyst, chiral ligand, base, solvent, and reaction temperature (see the Supporting Information for details) revealed that the best results were obtained with $[Cu(CH_3CN)_4]BF_4$ (5 mol%) in the presence of chiral ligand **L1** (6 mol%; (*R*)-3,5-*t*Bu$_2$-MeOBIPHEP) using

Table 1: Scope of the asymmetric [3+2] cycloaddition.[a]



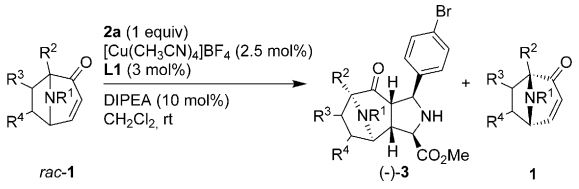
Entry	R^1	(−)-**3**	*t* [h]	Yield [%][b]	*ee* [%][c]
1	C_6H_5	(−)-**3b**	24	73	99
2	2-Me-C_6H_4	(−)-**3c**	24	70	98
3	3-Me-C_6H_4	(−)-**3d**	24	90	98
4	4-Me-C_6H_4	(−)-**3e**	24	80	>99
5	4-F-C_6H_4	(−)-**3f**	5	75	99
6	4-Cl-C_6H_4	(−)-**3g**	5	85	>99
7	4-Br-C_6H_4	(−)-**3a**	5	82	99
8	4-CF_3-C_6H_4	(−)-**3h**	5	78	99
9	4-CO_2Me-C_6H_4	(−)-**3i**	5	81	98
10[d]	4-MeO-C_6H_4	(−)-**3j**	24	74	97
11	3-MeO-C_6H_4	(−)-**3k**	24	87	97
12	3,4-di-MeO-C_6H_3	(−)-**3l**	24	64	97
13	4-Ph-C_6H_4	(−)-**3m**	24	74	>99
14	4-*t*Bu-C_6H_4	(−)-**3n**	24	55	97
15	2,3-di-Cl-C_6H_3	(−)-**3o**	5	91	99
16	1-naphthyl	(−)-**3p**	24	60	98
17	2-naphthyl	(−)-**3q**	24	76	98

[a] Reaction conditions: *rac*-**1a** (2.0 equiv), imine **2** (1.0 equiv, 0.1 mmol), DIPEA (20 mol%), $[Cu(CH_3CN)_4]BF_4$ (5 mol%), **L1** (6 mol%), CH_2Cl_2 (0.1 M), room temperature, until disappearance of the ester imines (5–24 h). [b] Yield of the isolated product after column chromatography. [c] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [d] *rac*-**1b** was used instead of *rac*-**1a**.

DIPEA (20 mol%) as the base in CH_2Cl_2 at room temperature (Scheme 1). Under these reaction conditions, the *exo*-cycloadduct (−)-**3a** was obtained in 82% yield with 99% *ee* (Scheme 1).

Having in hand the optimized reaction conditions, we investigated the scope of the [3+2] cycloaddition by treating tropane (*rac*-**1a**) with various glycine ester imines **2** (Table 1). The reaction was very versatile and displayed wide scope, with various functional groups on the phenyl ring of imines **2** tolerated (Table 1). Unfortunately, aliphatic imines were not reactive under the developed reaction conditions.

Table 2: Kinetic resolution of tropanes with azomethine ylides.[a]



Entry	*rac*-**1**	Conv. [%][b]	*ee* (yield) [%] of **3**[c]	*ee* (yield) [%] of **1**[c]	s[d]
1	*rac*-**1a**	51	99 (41)	97 (46)	119
2	*rac*-**1b**	50	98 (40)	94 (46)	115
3	*rac*-**1c**	51	94 (41)	91 (46)	47
4[e]	*rac*-**1d**	51	97 (45)	95 (42)	81
5	*rac*-**1e**	51	97 (44)	96 (44)	97
6[e]	*rac*-**1f**	52	96 (37)	99 (37)	116
7	*rac*-**1g**	51	97 (43)	97 (47)	119
8	*rac*-**1h**	50	99 (41)	94 (49)	115

[a] Reaction conditions: *rac*-**1** (0.2 mmol), imine **2a** (0.1 mmol), DIPEA (10 mol%), $[Cu(CH_3CN)_4]BF_4$ (2.5 mol%), **L1** (3 mol%), CH_2Cl_2 (1.0 mL), room temperature, until disappearance of the ester imines (5–24 h). [b] Determined by ^{1}H NMR spectroscopy. [c] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [d] Selectivity factors (s), s factor = Ln[(1-conv)(1-*ee*$_1$)]/Ln[(1-conv)(1 + *ee*$_1$)]. [e] *rac*-**1** (0.2 mmol), imine **2a** (0.105 mmol).

Despite the importance of optically enriched tropanes **1** as building blocks in organic synthesis,[7,8] only a few asymmetric catalytic methods have been developed for the synthesis of compounds based on the tropane scaffold.[9,12c] In particular, although there are several reports on the [5+2] cycloadditions of 3-oxidopyrylium betaines with alkenes for the synthesis of tropanes,[14,15] the corresponding catalytic enantioselective version has remained elusive. To our delight, the kinetic resolution of racemic starting material under the conditions of the enantioselective [3+2] cycloaddition described above is very efficient (Table 2). In general, cycloadducts (−)-**3** were obtained in yields of 37–45 % and with 94–99 % *ee* together with a 37–49 % yield of recovered starting material with 91–99 % *ee* (s factor: 47–119).

The efficiency of the kinetic resolution encouraged us to investigate whether this transformation would enable an enantiodivergent synthesis. We hypothesized that if racemic tropane (**1**) was subjected to a sequence of cycloadditions with two different azomethine ylides, two different enantiomerically highly enriched products could be obtained in a one-pot reaction, and, importantly, with only one chiral ligand (Figure 2). In the first step, 1,3-dipolar cycloaddition with one given azomethine ylide would provide the cycloadduct (−)-**3** and enantioenriched tropane (+)-**1** (Figure 2). A diastereoselective 1,3-dipolar cycloaddition reaction of (+)-**1** with a second azomethine ylide would then provide cycloadduct (+)-**3′**. We envisioned the use of two azomethine ylides with differing polarity ($R^2 \neq R^3$, Figure 2) to enable straightforward separation of the two products ((−)-**3** and (+)-**3′**) by column chromatography.

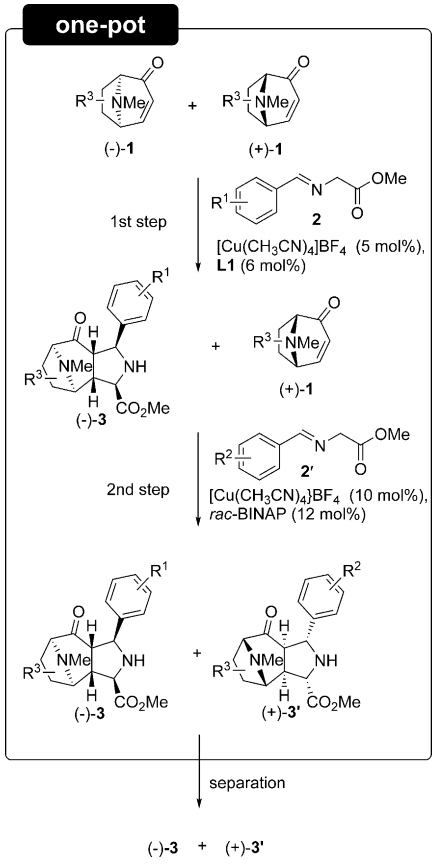
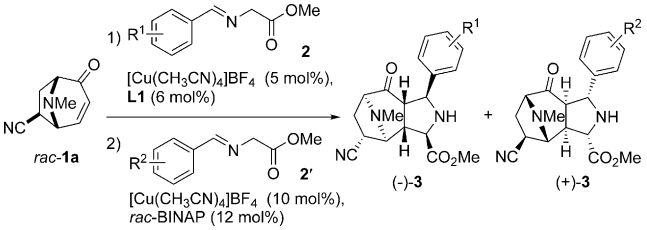


Figure 2. Enantiodivergent synthesis. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

To our delight, the one-pot sequence designed accordingly proceeds with high efficiency if a combination of [Cu(CH_3CN)$_4$]BF_4 (10 mol %) and *rac*-BINAP (12 mol %) is employed as the catalyst for the second cycloaddition. For a variety of imines the two enantiomers were obtained in 33–49 % yield and with 88–99 % *ee* (Table 3, entries 1–6). Notably, formation of the respective opposite enantiomers can easily be achieved by simply switching the order of the imine addition (Table 3, entries 6 and 7). The absolute configuration of a representative cycloadduct was determined by X-ray diffraction (see the Supporting Information), and the absolute configurations of all other compounds were assigned by analogy.

Table 3: Enantiodivergent tropane synthesis by means of sequential [1,3]-dipolar cycloaddition.[a]



Entry	R^1	R^2	(−)-**3** *ee* (yield) [%][b]		(+)-**3** *ee* (yield) [%][b]	
1	4-Br	4-CO_2Me	(−)-**3a**	98 (48)	(+)-**3i**	95 (48)
2	4-CO_2Me	4-Me	(−)-**3i**	98 (43)	(+)-**3e**	91 (42)
3	3-OMe	3-Me	(−)-**3k**	97 (42)	(+)-**3d**	88 (49)
4	3-Me	3,4-di-OMe	(−)-**3d**	95 (44)	(+)-**3l**	97 (33)
5	4-Ph	4-OMe	(−)-3 m	99 (49)	(+)-**3y**	90 (46)
6	4-OMe	2,3-di-Cl	(−)-**3y**	98 (40)	(+)-**3o**	94 (48)
7	2,3-di-Cl	4-OMe	(−)-**3o**	97 (42)	(+)-**3y**	94 (48)

[a] Reaction conditions: Step 1: imine **2** (1.0 equiv, 0.1 mmol), tropane **1** (2.0 equiv), DIPEA (20 mol %), [Cu(CH_3CN)$_4$]BF_4 (5 mol %), **L1** (6 mol %), CH_2Cl_2 (1.0 mL), room temperature, until disappearance of the ester imines (5–24 h); Step 2: imine **2′** (1.5 equiv, 0.15 mmol), [Cu(CH_3CN)$_4$]BF_4 (10 mol %), *rac*-BINAP (12 mol %), CH_2Cl_2 (1.0 mL), room temperature, 4 h. [b] Yield of the isolated product after column chromatography; the *ee* value was determined by HPLC analysis on a chiral stationary phase.

In conclusion, we report the development of an efficient enantiodivergent synthesis of natural product inspired hybrid compounds with a maximum of eight stereocenters from simple starting materials. The obtained products embody two privileged natural products fragments, namely the tropane and the pyrrolidine scaffold. The synthesis proceeds with high diastereo- and enantioselectivity and has broad substrate scope. Importantly, this method enables two opposing enantiomers to be readily synthesized by employing only one chiral ligand in a one-pot reaction and using a single flash chromatographic separation.

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Keywords: asymmetric catalysis · cycloaddition · enantiomers · kinetic resolution · tropane

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