Organocatalysis

DOI: 10.1002/anie.201002485

Enantioselective Phase-Transfer Catalysis: Synthesis of Pyrazolines**

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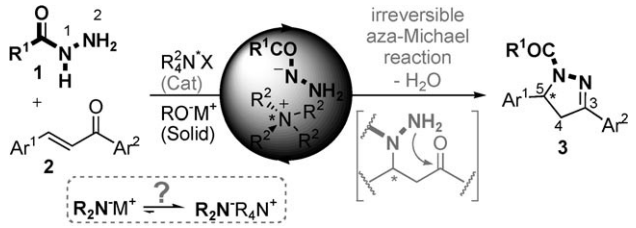
The development of asymmetric catalytic reactions, as cost-effective and environmentally friendly methodologies, is a response to the increased demand of pharmaceutically relevant chiral aza-heterocycles.[1] In this context, the Δ^2-pyrazolinyl platform is the core structure of many bioactive ingredients, and among them are the recurring 3,5-diarylpyrazoline architectures **3** (Scheme 1),[2] which have a polar group on N1.[3] However, an efficient enantioselective synthesis of this type of 4,5-dihydropyrazoles remains elusive.



Scheme 1. Organocatalytic strategy using chiral ammonium/amide ion pairs.

The first catalytic enantioselective construction of pyrazolines, which was reported in 2000, proceeds through 1,3-dipolar cycloaddition reactions of acrylamides by means of Lewis acidic magnesium complexes.[4] The subsequently developed asymmetric approaches were dominated by organometallic strategies which encompass [2+3] cycloadditions of either diazoalkane dipoles[5] or nitrile imine dipole precursors, as well as others.[6,7] Alternatively, Kanemasa and Yanagita described a metal-promoted aza-Michael cyclocondensation cascade using electron-rich *N*-arylhydrazines to give exclusively 3-pyridyl-4-aryl pyrazolines, albeit with moderate enantioselectivity.[8] This example, to our knowledge, constitutes the only attempt to construct nonracemic 3,5-diaryl pyrazolines. The organocatalytic asymmetric synthesis of *N*-aryl pyrazolines was pioneered by List and Müller by making use of an elegant 6 π electrocyclization.[9] This recent achievement paves the way for the development of original transition-metal-free synthetic strategies that are suited to the elaboration of pharmaceutically relevant chiral heterocycles.

To provide efficient access to the chiral nonracemic 3,5-diarylpyrazoline **3** (Scheme 1), bearing a polar group on N1 [usually an electron-withdrawing group (EWG)], we envisaged a domino aza-Michael addition/cyclocondensation reaction of electron-poor hydrazine anions with chalcones catalyzed by a chiral quaternary ammonium salt.[10] We assumed that an irreversible (nonracemizing) conjugate addition of deprotonated acylhydrazines would be secured by the subsequent imine bond formation.[11] However, the formation of an effective chiral ion pair between an amide anion and an ammonium salt through cation exchange (M^+/R_4N^+) remained questionable, but was required to prevent a racemic background process. Thus far, phase-transfer catalysis (PTC) has elicited robust organocatalytic strategies for the asymmetric construction of C–C bonds from C anions and, to a lesser extent, C–X bonds from anionic O and S nucleophiles.[12] Nonetheless, the examples of asymmetric PTC approaches for C–N bond formation using anionic N-nucleophilic species are rare.[10,12,13] In the 1970s, Juliá et al. pioneered the kinetic resolution of chiral tertiary alkyl bromides by using potassium phthalimide nucleophiles under the influence of cinchonium-derived alkaloids albeit with modest selectivities.[14] Later in 1996, preliminary investigations from Prabhakar and co-workers triggered a series of studies dealing with the asymmetric aziridination reactions of enones by O-substituted hydroxylamide anions,[15a–d] and then later extended to *N*-chloro-*N*-sodio carbamate.[15e] Recently, a useful intramolecular enantioselective conjugate addition of deprotonated indoles to an acrylate was achieved under PTC conditions.[16] We describe herein an unprecedented asymmetric synthesis of pyrazolines under PTC reaction conditions by making use of the R_2N^-/R_4N^+ ion pairing mode of activation.[17]

We first carried out a set of reactions between chalcone (**2a**) and *N*-*tert*-butyloxycarbonyl hydrazine **1a** (1.1 equiv) in the presence of potassium carbonate (solid–liquid phase-transfer conditions) and various commercially or easily available chiral ammonium salts derived from cheap cinchona alkaloids (Table 1).[12c] Pleasingly, 10 mol% of *N*-benzyl quininium **4a** furnished (*S*)-(−)-pyrazoline **3a** with a promising 67% *ee* albeit in 31% yield. Subsequent attempts revealed that the presence of water (liquid–liquid phase-transfer conditions with **4a**; Table 1 < xtabr1, entry 2) and the use of cinchonidinium salt **4b** were detrimental to the enantiomeric excess. Interestingly, the introduction of an

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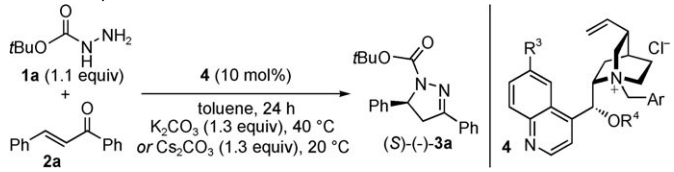
[**] We gratefully acknowledge financial support from the Région Haute-Normandie and the CRUNCH network (Centre de Recherche Universitaire Normand de Chimie), as well as the Ministère de la Recherche and CNRS (Centre National de la Recherche Scientifique).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201002485.

Table 1: Optimization of the reaction.



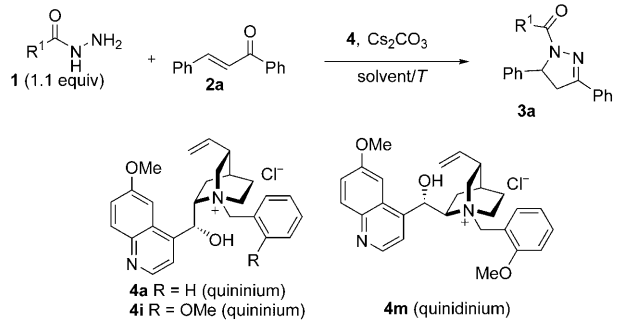
Entry	4	R^3	R^4	Ar	Base/T [°C]	Yield [%][a]	*ee* [%][b]
1	**4a**	OMe	H	Ph	K_2CO_3/40	31	67
2	**4a**	OMe	H	Ph	K_2CO_3/40	20[c]	57
3	**4b**	H	H	Ph	K_2CO_3/40	11	48
4	**4c**	OMe	allyl	Ph	K_2CO_3/40	17	20 (*R*)[d]
5	**4a**	OMe	H	Ph	Cs_2CO_3/20	55	73
6	**4d**	OMe	H	anthracenyl	Cs_2CO_3/20	15	12 (*R*)[d]
7	**4e**	OMe	H	4-$MeOC_6H_4$	Cs_2CO_3/20	58	56
8	**4f**	OMe	H	4-$CF_3C_6H_4$	Cs_2CO_3/20	38	54
9	**4g**	OMe	H	4-FC_6H_4	Cs_2CO_3/20	46	61
10	**4h**	OMe	H	2-FC_6H_4	Cs_2CO_3/20	72	79
11	**4i**	OMe	H	2-$MeOC_6H_4$	Cs_2CO_3/20	80	80
12	**4j**	OMe	H	2-MeC_6H_4	Cs_2CO_3/20	54	68
13	**4k**	OMe	H	2-pyridyl	Cs_2CO_3/20	48	24
14	**4l**	OMe	H	2-pyridyl-*N*-oxide	Cs_2CO_3/20	84	65

[a] Yield of pyrazine **3a** determined by NMR methods using an internal standard. [b] Determined by HPLC analysis using a chiral stationary phase. [c] Toluene/H_2O (75:25) used as solvent. [d] Absolute configuration determined by comparison to analogue **6a**; see Ref. [21].

allylic functional group on the alcohol at C9 (**4c**) or using the bulkier anthracenyl derivative **4d** led to an reversal of the enantioselectivity and low-yielding reactions. Apparently, the suitable organization of the amide/ammonium ion pair that leads to efficient chirality transfer during the C–N bond formation requires the presence of a free alcohol at C9. Futhermore, the steric hindrance at the benzylic moiety of the quinuclidinium structure appeared to be a limiting structural feature as exemplified by the catalyst **4d**. At this stage, it was found that the use of cesium carbonate instead of potassium carbonate improved the yields (from 31% to 55% for catalyst **4a**) while allowing the lowering of the reaction temperature from 40°C to 20°C (67% to 73% *ee* for catalyst **4a**). Then, we turned our attention to electronic effects and tested catalysts having *para*-substituted benzylic rings (**4e**–**4g**), but disappointing results were obtained. Recently, Jew, Park, and coworkers pioneered *ortho*-substituted benzyl cinchona derivatives such as **4h** as potent catalysts for glycine alkylation.[18] Such catalysts were successfully exploited by Ricci and coworkers, who used *ortho*-methoxy benzyl ammonium salts such as **4i** in several elegant PTC processes.[19] In our hands, the enantiomeric excesses were improved from 73% *ee* with quininium **4a** to 79% *ee* with *ortho*-fluorobenzyl compound **4h**, and a faster reaction was achieved such that pyrazoline **3a** was isolated in 72% yield after 24 hours. The best results (80% *ee*) were obtained with quininium salt **4i**, which possesses a free alcohol and an *ortho*-methoxybenzyl motif. In this regard, structure–activity relationships were examined and revealed that the 2-methyl-substituted catalyst **4j** furnished only 68% *ee*, thereby excluding a simple steric influence on selectivity. The comparison of the activity between the 2-pyridyl **4k** and 2-pyridyl-*N*-oxide **4l** derivatives shows that a polar functional group at the *ortho* position of the benzylic substructure is required; this polar group (e.g., *N*-oxide) is likely to accept hydrogen bonds which in turn results in improved yields and *ee* values. Nevertheless, catalysts **4k** and **4l** containing a pyridine ring resulted in a less enantioselective reaction (see the Supporting Information for further details).[18]

To investigate the scope of the reaction, we examined the EWG on the hydrazine ($R^1CONHNH_2$) in the presence of catalyst **4a** (Table 2). Although the *N*-benzoyl hydrazine

Table 2: Optimization with various hydrazines $R^1CONHNH_2$ **1**.[a]



Entry	Cat.	R^1	Solvent/*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**4a**	Ph	toluene/RT	0	–
2	**4a**	Me	toluene/RT	86	9
3	**4a**	OEt	toluene/RT	74	26
4	**4a**	OBn	toluene/RT	60	26
5	**4a**	O*t*Bu	toluene/RT	55	73 (*S*)
6	**4a**	O*t*Bu	toluene/0	55	78 (*S*)
7	**4a**	O*t*Bu	toluene/−20	45	23 (*S*)
8	**4i**	O*t*Bu	THF/0	80	92 (*S*)
9	**4m**	O*t*Bu	THF/0	78	92 (*R*)
10[d]	**4i**	O*t*Bu	THF/0	77	93 (*S*)[e]

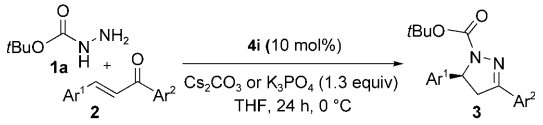
[a] Reaction conditions: chalcone **2a** (0.5 mmol), hydrazine **1** (1.1 equiv), Cs_2CO_3 (1.3 equiv), and 10 mol% of catalyst **4** for 24 h. [b] Yield of pyrazoline **3a** determined by NMR methods using an internal standard. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Carried out with chalcone **2a** (2 mmol), 2 mol% of catalyst **4i** and 0.5 equivalents of Cs_2CO_3 for 87 h giving 70% yield of the isolated product after column chromatography (43% yield in 24 h). [e] Greater than 99% *ee* after one recrystallization in EtOAc/petroleum ether (1:3). Bn = benzyl.

(Table 2, entry 1) did not yield the pyrazoline product **3a**, the *N*-acetyl derivative (Table 2, entry 2) smoothly reacted with chalcone **2a** to give the corresponding pyrazoline in 86% yield, but low selectivity was measured. The bulky *N*-Boc hydrazine was the only carbamate derivative (Table 2, entries 3–5) to achieve a significant *ee* value in its reaction, thereby showing the subtle influence of both the steric hindrance and pK_a value of the hydrazine nucleophiles upon these asymmetric aza-Michael reactions. The enantiomeric excesses were slightly improved at 0°C (Table 2, entry 6), but a lower temperature was detrimental to the reaction (Table 2, entry 7). Consequently, by using the more competent *ortho*-methoxy quininium catalyst **4i** (see the Supporting Information) in THF at 0°C, the efficient formation of pyrazoline **3a** was observed in 80% yield with 92% *ee* (Table 2, entry 8).

Most importantly, the pseudo-enantiomeric effect was fully countered by means of using 10% of the quinidinium catalyst **4m** (Table 2, entry 9), which allowed the construction of (*R*)-**3a**. We also demonstrated that on a 2 mmol scale only 0.5 equivalents of Cs_2CO_3 and 2 mol% of catalyst **4i** (Table 2, entry 10) were needed to maintain the high enantioselectivity (93% *ee*), but the reaction required 87 hours to reach completion. As a practical issue for the synthesis of chiral drugs, a virtually enantiopure pyrazoline **3a** could be obtained after one recrystallization (Table 2, entry 10).

We evaluated these user-friendly and cost-effective organocatalytic conditions by applying them to reactions of chalcone derivatives (**2**) with a quasi-stoichiometric amount of **1a** (Table 3). Pyrazolines **3** having various aryl (Table 3, entries 1–6 and 9) and heterocyclic (Table 3, entries 7 and 8) substituents at C3 were formed with more than 90% *ee*. As a general trend, it was found that K_3PO_4 slightly improved the enantiomeric excesses relative to those obtained with Cs_2CO_3 (Table 3, entries 4, 6, and 8), but the reactions were slower and the yields were lower after the same reaction time (24 hours). The *ortho, meta,* and *para* substitution on the aryl rings at C5 were well tolerated even though a slight drop in the *ee* values was measured (Table 3, entries 10–13). The thienyl heterocycle led to a lower enantiomeric excess (Table 3, entry 14).[20]

Table 3: Scope of the enantioselective synthesis of pyrazolines.[a]

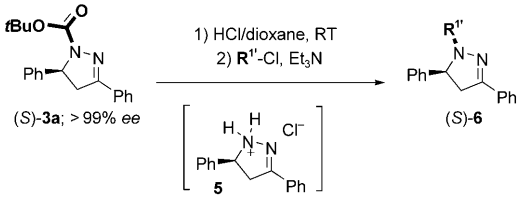


Entry	Base	Ar^1	Ar^2	Yield [%][b]	*ee* [%][c]
1	Cs_2CO_3	Ph	Ph	77	92 (−)
2	Cs_2CO_3	Ph	4-$MeOC_6H_4$	71	90 (−)
3	Cs_2CO_3	Ph	4-FC_6H_4	72	90 (−)
4	K_3PO_4	Ph	4-FC_6H_4	62	92 (−)
5	Cs_2CO_3	Ph	2-$MeOC_6H_4$	89	92 (−)
6	K_3PO_4	Ph	2-$MeOC_6H_4$	52	94 (−)
7	Cs_2CO_3	Ph	2-thienyl	66	87 (−)
8	K_3PO_4	Ph	2-thienyl	60	91 (−)
9	K_3PO_4	Ph	3,4-$Cl_2C_6H_3$	40 (62)[d]	92 (−)
10	K_3PO_4	4-$MeOC_6H_4$	Ph	60	89 (+)
11	K_3PO_4	4-ClC_6H_4	Ph	70	88 (−)
12	K_3PO_4	2-MeC_6H_4	Ph	62	89 (−)
13	K_3PO_4	3-$MeOC_6H_4$	Ph	61	91 (−)
14	K_3PO_4	2-thienyl	Ph	46	78 (−)

[a] Reactions were performed on a 0.5 mmol scale of chalcones **1** with 1.1 equivalent of hydrazine **1a**. [b] Yield of isolated product after column chromatography. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Yield determined by NMR analysis of the crude reaction mixture using an internal standard.

The use of **1a** was key to the success of this enantioselective synthesis of the 3,5-diaryl pyrazolines, but the methodology is restricted to the formation of *N*-Boc derivatives. Nevertheless, we achieved a practical one-pot protecting-group exchange by making use of the acid lability of the *N*-Boc group, thereby extending the scope of this methodology (Table 4). A straightforward construction of **6a–c** (Table 4, entries 1–3) and diastereoisomeric **6d** (Table 4, entry 4) was realized, without any racemization, starting from the enantioenriched pyrazoline **3a** (see Table 2, entry 10). Considering the usual chemical and configurational instability of 1*H*-pyrazolines through oxidative degradation pathways,[11] this achievement is noteworthy. The formation of an ammonium intermediate **5** is likely and prevents any decomposition. Pleasingly, the resulting product **6a** (Table 4, entry 1) was crystalline and the absolute configuration at C5 of the pyrazoline ring was determined to be *S* as confirmed by X-ray diffraction methods.[21]

Table 4: One-pot protecting-group exchange.



Entry	Product	$R^{1'}$	Yield [%][a]	Selectivity[b]
1	**6a**	Ts	86	> 99% *ee* (−)
2	**6b**	Ac	99	> 99% *ee* (−)
3	**6c**	Bz	99	> 99% *ee* (−)
4	**6d**	camphor sulfonyl	93	> 99% *de*[c]

[a] Yield of product isolated after column chromatography. [b] Determined by HPLC analysis using a chiral stationary phase. [c] Determined by ^{1}H NMR analysis. Bz = benzoyl, Ts = 4-toluenesulfonyl.

With the *ortho*-fluorobenzyl ammonium catalyst **4h** Jew, Park, and co-workers demonstrated, by using X-ray crystal diffraction, that a molecule of water was bound between the oxygen atom on C9 and the *ortho*-fluorine atom on the benzyl moiety.[18] The authors proposed that preorganization of the obtained complex leads to improvement of the chiral induction. In our case, however, hydrated conditions yielded a drop in the *ee* values.[22] We suppose instead that both OH and OMe functional groups of quininium catalyst **4i** are synergistically involved in a hydrogen-bond network around the nucleophilic hydrazine anion of **1a**, thus providing a useful chiral platform for the selection of the prochiral enone faces en route to an effective asymmetric synthesis of pyrazolines (see the Supporting Information).[23] This hypothesis is currently under investigation.

In conclusion, we developed an original and straightforward enantioselective synthesis of 3,5-diaryl pyrazolines, biorelevant aza-heterocycles, by using phase-transfer organometallic methodology. The discovery that an *N*-*ortho*-methoxybenzyl quininium salt leads to a useful chiral ammonium/amide ion pair from *N*-acylhydrazines in this process has prompted investigations of its utility for other asymmetric transformations.

Received: April 26, 2010
Revised: June 23, 2010
Published online: August 16, 2010

Keywords: asymmetric synthesis · heterocycles · Michael addition · organocatalysis · phase-transfer catalysis

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[20] The present methodology did not furnish pyrazoline derivatives from aliphatic ketones. For instance, the *trans*-1-phenyl-2-buten-1-one mainly dimerized and gave a little of the aza-Michael product resulting from the conjugate addition of the primary amine of the *tert*-butylcarbazate. For precedent, see: F.-Y. Zhang, E.-J. Corey, *Org. Lett.* **2004**, *6*, 3397.

[21] CCDC 773701 contains the supplementary crystallographic data of pyrazoline (*S*)-(−)-**6a** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The absolute configurations of the remaining pyrazolines as *levo* (−) isomer were assigned (*S*) by analogy to **6a**. The only one exception to this rule is 5-(4-methoxyphenyl)-3-phenyl-pyrazoline (Table 2, entry 10).

[22] The *ortho*-fluorobenzyl catalyst **4h** with K_2CO_3 at 40 °C gave pyrazoline **3a** in 72% *ee* in toluene and 57% *ee* in a mixture of toluene/H_2O (75:25).

[23] For insight into role of the hydrogen bonds with ammonium PTC, see: E. Gomez-Bengoa, A. Linden, R. López, I. Múgica-Mendiola, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2008**, *130*, 7955.

