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Phase-Transfer-Catalyst-Mediated Domino Reaction of γ-Nitro Ketones with Chalcones: Approach to Functionalized Six-Membered-Ring Carbocycles

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Keywords: Synthetic methods / Phase-transfer catalysis / Cyclization / Domino reactions / Aldol reactions / Michael addition / Enones

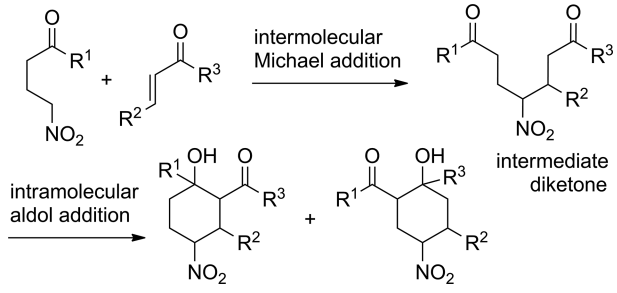
Domino reactions between γ-nitro ketones and chalcones for the construction of functionalized six-membered-ring carbocycles using a phase-transfer catalyst have been developed. In the presence of tetrabutylammonium iodide and potassium hydroxide, domino reactions between γ-nitro ketones and a series of chalcones proceeded smoothly to give the cyclic products in moderate to high yields with high diastereoselectivities. Importantly, multiply substituted and functionalized six-membered-ring carbocycles could be efficiently prepared in one pot using this domino strategy.

Introduction

Six-membered-ring carbocycles are widespread in natural products and other important biologically active compounds.[1] Functionalized six-membered-ring carbocycles also act as building blocks in synthetic chemistry.[2] Due to the importance of six-membered-ring carbocycles, much effort has been devoted to this field.[3]

Domino reactions have a high synthetic efficiency as they allow the number of laboratory operations required and the quantities of chemicals and solvents used to be decreased. As a result, they have attracted great interest, and they are continually used in organic synthesis.[4] Such domino reactions represent an efficient method for the synthesis of a wide range of complex molecules, including natural products and biologically active compounds such as agrochemicals and pharmaceuticals.[5]

Very recently, we developed an efficient catalytic domino reaction between aldehydes and ketones for the synthesis of cyclohexenone derivatives.[6] Continuing our investigations in this field, we have used this domino strategy in the reaction between γ-nitro ketones and α,β-unsaturated ketones (enones) for the construction of functionalized six-membered-ring carbocycles. A γ-nitro ketone was expected to react with an enone to give an intermediate diketone, and then an intramolecular aldol reaction of the intermediate diketone would give the functionalized six-membered-ring carbocycles (Scheme 1).



Scheme 1. Domino strategy for the construction of functionalized six-membered-ring carbocycles.

Phase-transfer catalysis has received much attention and been recognized as one of the most versatile and powerful methods for organic synthesis in both academia and industry.[7,8] The advantages of this approach include operational simplicity, mild reaction conditions, the use of low-cost and environmentally friendly starting materials, and so on. Impressive results have been achieved in the field of cyclization under phase-transfer catalysis.[9] To our delight, the domino reaction between chalcones and γ-nitro ketones could also be accomplished under phase-transfer catalysis to construct functionalized six-membered-ring carbocycles. Compared with other domino processes involving Michael-type reactions either of nitroalkenes[10] or α,β-unsaturated carbonyl compounds[11] for the synthesis of these functionalized skeletons, this alternative method has several advantages, such as the availability of the reactants, low catalyst loading, mild reaction conditions, low cost, and high efficiency. Furthermore, phase-transfer catalysis could mediate certain reactions of esters, nitriles, and nitro compounds for which other organocatalysts do not work. In this paper, we present

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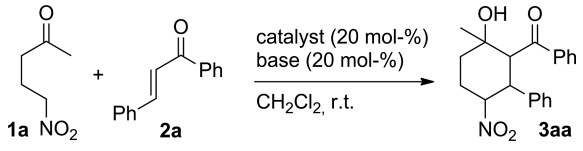
this phase-transfer-catalyst-mediated domino reaction between chalcones and γ-nitro ketones for the construction of functionalized six-membered-ring carbocycles.

Results and Discussion

At the outset of our initial investigation, we focused on the domino reaction between 5-nitropentan-2-one (**1a**) and chalcone (**2a**). Using DBU (1,8-diazabicycloundec-7-ene) as base without phase-transfer catalyst, annulation product **3aa** was obtained in 61% yield with >95% *dr* from the domino reaction between chalcone and 5-nitropentan-2-one (Table 1, entry 1). DABCO (1,4-diazabicyclo[2.2.2]octane) did not promote the domino reaction (Table 1, entry 2). When K_2CO_3 was used as a base, product **3aa** was obtained in 66% yield with similar diastereoselectivity after a long reaction time (Table 1, entry 3). A remarkable enhancement in yield without compromising the diastereoselectivity was achieved when a phase-transfer catalyst, tetrabutylammonium bromide (Bu_4NBr), was introduced into the reaction mixture (Table 1, entry 4). A screening of bases was then carried out (Table 1, entries 5–10) and a combination of Bu_4NBr and KOH was found to give the best results, 76% yield after 1.5 h (Table 1, entry 8). A further screening of phase-transfer catalysts revealed that up to 86% yield could be obtained within 5 h from a Bu_4NI/KOH-mediated domino reaction between chalcone and 5-nitropentan-2-one (Table 1, entry 13). These encouraging results indicated that a phase-transfer catalyst/base combination might be a very efficient tool for this kind of domino reaction. Importantly, functional groups such as hydroxy groups,[12] nitro groups,[13] and carbonyl groups[14] on the ring could easily be transformed into other functional groups, which makes these six-membered-ring carbocycles more valuable in synthetic chemistry.

Table 1. Screening catalysts and bases for the domino reaction.



Entry[a]	Catalyst	Base	Time [h][b]	Yield [%][c]	*dr* [%][d]
1	–	DBU	18	61	>95
2	–	DABCO	72[e]	trace	–
3	–	K_2CO_3	120[e]	66	>95
4	Bu_4NBr	K_2CO_3	15	70	>95
5	Bu_4NBr	Cs_2CO_3	1.5	70	>95
6	Bu_4NBr	LiOH	96[e]	39	>95
7	Bu_4NBr	NaOH	24	61	>95
8	Bu_4NBr	KOH	1.5	76	>95
9	Bu_4NBr	$Ba(OH)_2$	96[e]	trace	–
10	Bu_4NBr	*t*BuOK	0.33	72	>95
11	Bu_4NF	KOH	0.5	76	>95
12	Bu_4NCl	KOH	0.83	67	>95
13	Bu_4NI	KOH	5	86	>95

[a] Unless otherwise noted, the reaction was carried out as follows: 5-Nitropentan-2-one (**1a**; 0.6 mmol) and chalcone (**2a**; 0.5 mmol) were mixed in CH_2Cl_2 (1 mL). Base (20 mol-%) and phase-transfer catalyst (20 mol-%) were added, and the reaction mixture was stirred at room temperature for the time given in the Table. [b] After this time, **2a** was fully consumed, and the reaction mixture was then worked up. [c] Isolated yield. [d] Diastereomeric ratio based on ^1H NMR analysis. [e] After this time, **2a** was not fully consumed, but the reaction mixture was still worked up.

It should be noted that all the reactions tested gave annulation product **3aa** with excellent diastereoselectivities, as confirmed by ^1H NMR spectroscopic analysis. Furthermore, annulation product **3al** from the Bu_4NI/KOH-mediated domino reaction between 5-nitropentan-2-one (**1a**) and (*E*)-3-(4-bromophenyl)-1-(3-chlorophenyl)prop-2-en-1-one (**2l**) was unequivocally identified by X-ray analysis as a pair of enantiomers of [(1*S*,2*R*,5*S*,6*R*)-6-(4-bromophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl](3-chlorophenyl)methanone and [(1*R*,2*S*,5*R*,6*S*)-6-(4-bromophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl](3-chlorophenyl)methanone (**3al**; Figure 1).[15] The high stereoselectivity is probably due to an initial highly diastereoselective Michael addition of γ-nitro ketone to chalcone. The product of the Michael addition presumably dictates the stereochemistry of the subsequent aldol reaction. The configurations of the hydroxy group and 3-ClPhCO groups are *syn*, and there is an intramolecular hydrogen bond between the hydroxy group and the carbonyl of the 3-ClPhCO group. A plausible mechanism for the formation of **3al** is shown in Scheme 2. The initial Michael addition of **1a** to **2l** gave a pair of enantiomers with high diastereoselectivity. This was followed by an aldol reaction to give (1*S*,2*R*,5*S*,6*R*)- and (1*R*,2*S*,5*R*,6*S*)-**3al**.

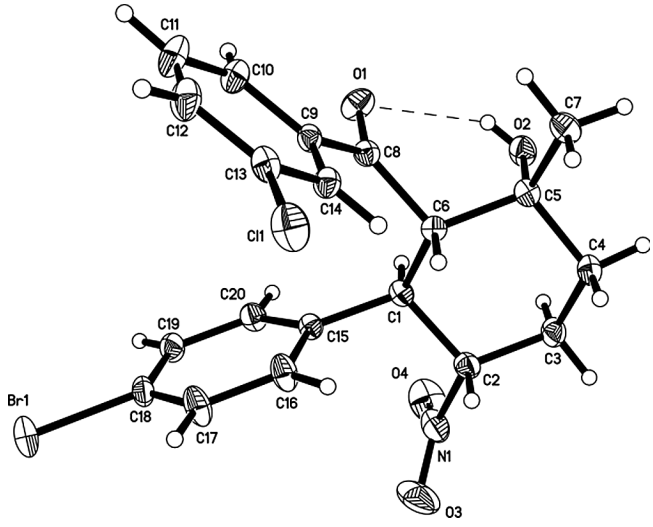
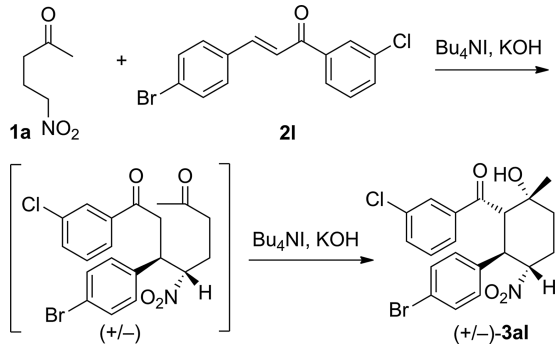


Figure 1. X-ray crystal structure of annulation product **3al**.

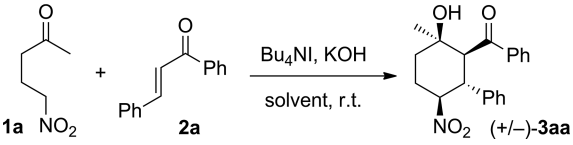
Having identified the best catalytic system, optimization of reaction conditions was then investigated and representative results are listed in Table 2. Commonly used organic solvents were examined first. It should be noted that all the solvents tested gave functionalized six-membered-ring carbocycle **3aa** in good yield and with excellent diastereoselectivity within an acceptable reaction time (Table 2, entries 1–8). In MeCN, the desired product (i.e., **3aa**) was



Scheme 2. Proposed mechanism for the domino reaction.

formed in 90% yield with excellent diastereoselectivity after 1 h (Table 2, entry 6). The best results, 93% yield and >95% *dr*, were obtained when the domino reaction was carried out in EtOAc for 3 h (Table 2, entry 7).

Table 2. Optimization of reaction conditions.



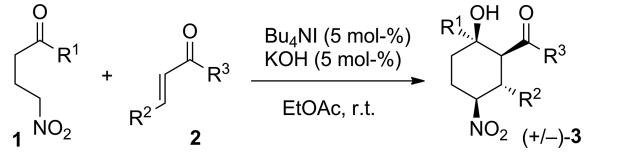
Entry[a]	Bu_4NI [mol-%]	KOH [mol-%]	Solvent	Time[b] [h]	Yield[c] [%]	*dr*[d] [%]
1	20	20	CH_2Cl_2	5	86	>95
2	20	20	THF	2	86	>95
3	20	20	MeOH	10	78	>95
4	20	20	Et_2O	11	84	>95
5	20	20	toluene	8	73	>95
6	20	20	MeCN	1	90	>95
7	20	20	EtOAc	3	93	>95
8	20	20	DMF	1	79	>95
9	15	20	EtOAc	3	96	>95
10	10	20	EtOAc	3	87	>95
11	5	20	EtOAc	3.5	92	>95
12	0	20	EtOAc	4	79	>95
13	5	15	EtOAc	3.5	92	>95
14	5	10	EtOAc	4.5	93	>95
15	5	5	EtOAc	6	94	>95

[a] Unless otherwise noted, the reaction was carried out as follows: 5-Nitropentan-2-one (**1a**; 0.6 mmol) and chalcone (**2a**; 0.5 mmol) were mixed in the solvent (1 mL). KOH and Bu_4NI were added, and the reaction mixture was stirred at room temperature for the time given in the Table. The configuration of **3aa** was derived from compound **3al**. [b] After this time, **2a** was fully consumed, and the reaction mixture was then worked up. [c] Isolated yield. [d] Diastereomeric ratio based on ^1H NMR analysis.

A further study was carried out to test different amounts of base and catalyst loadings. Lowering the catalyst loading still gave satisfactory yields and diastereoselectivities (Table 2, entries 9–11). With a catalyst loading of 5 mol-%, annulation product **3aa** was obtained in 92% yield after 3.5 h (Table 2, entry 11). In the presence of KOH but without a phase-transfer catalyst, the domino reaction gave cyclic product **3aa** in 79% yield after 4 h (Table 2, entry 12), yields of >90% and excellent diastereoselectivities could be still obtained when less base was used after an extended reaction time (Table 2, entries 13–15). For example, the domino reaction gave functionalized six-membered-ring carbocycle **3aa** in 94% yield with >95% *dr* after 6 h when Bu_4NI (5 mol-%) and KOH (5 mol-%) were used (Table 2, entry 15).

Under the optimal reaction conditions, Bu_4NI/KOH-catalyzed domino reactions between γ-nitro ketones **1** and a series of enones **2** were surveyed. All the domino reactions tested proceeded smoothly to give the functionalized six-membered-ring carbocycles **3** in moderate to high yields with excellent diastereoselectivities. Various substituents, either electron-withdrawing (-F, -Cl, -Br, $-NO_2$, $-CF_3$) or electron-donating (-Me, -OMe) groups, could be introduced into both of the aromatic rings of chalcone. The introduction of electron-withdrawing groups into either of the aromatic rings of chalcone led to high reaction rates (Table 3, entries 2–6, 9, and 12). On the other hand, extended reaction times were necessary for the formation of cyclic products **3** in acceptable yield when electron-donating groups were introduced into either of the aromatic rings of chalc-

Table 3. Scope of the domino reaction.

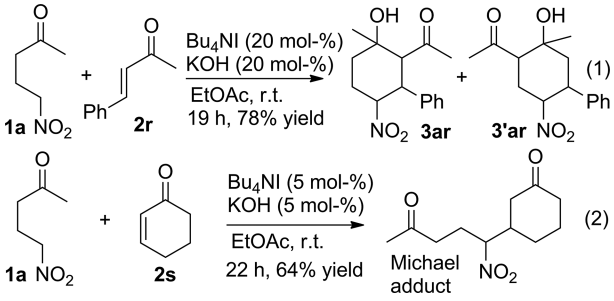


Entry[a]	R^1	R^2	R^3	Time[b] [h]	Yield[c] [%]	*dr*[d] [%]
1	Me	Ph	Ph	6	94, **3aa**	>95
2	Me	4-FC_6H_4	Ph	4	86, **3ab**	>95
3	Me	3-BrC_6H_4	Ph	3	90, **3ac**	>95
4	Me	4-BrC_6H_4	Ph	5	70, **3ad**	>95
5	Me	4-$O_2NC_6H_4$	Ph	1.5	71, **3ae**	>95
6	Me	4-$CF_3C_6H_4$	Ph	3	92, **3af**	>95
7	Me	4-MeC_6H_4	Ph	15	85, **3ag**	>95
8	Me	4-$MeOC_6H_4$	Ph	36	84, **3ah**	>95
9	Me	Ph	3-ClC_6H_4	3	80, **3ai**	>95
10	Me	Ph	4-$O_2NC_6H_4$	1.5	49, **3aj**	>95
				20[e]	67, **3aj**	
11	Me	Ph	3-$MeOC_6H_4$	19	61, **3ak**	>95
12	Me	4-BrC_6H_4	3-ClC_6H_4	2	67, **3al**	>95
13	Me	3-$O_2NC_6H_4$	4-$MeOC_6H_4$	18	75, **3am**	>95
14	Me	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	23	57, **3an**	>95
15	Me	4-MeC_6H_4	4-$O_2NC_6H_4$	2.5	81, **3ao**	>95
16	Me	4-MeC_6H_4	4-$MeOC_6H_4$	144[f]	60, **3ap**	>95
17	Me	4-$MeOC_6H_4$	3-ClC_6H_4	5	86, **3aq**	>95
18	Et	Ph	Ph	8	93, **3ba**	>95

[a] Unless otherwise noted, the reaction was carried out as follows: γ-Nitro ketone (**1**, 0.6 mmol) and enone (**2a**, 0.5 mmol) were mixed in EtOAc (1 mL). KOH (5 mol-%) and Bu_4NI (5 mol-%) were added, and the reaction mixture was stirred at room temperature for the time given in the Table. The configurations of products **3** were derived from compound **3al**. [b] After this time, **2a** was fully consumed, and the reaction mixture was then worked up. [c] Isolated yield. [d] Diastereomeric ratio based on ^1H NMR analysis. [e] The reaction was carried out at 0 °C. [f] After this time, enone **2** was not fully consumed, but the reaction mixture was still worked up.

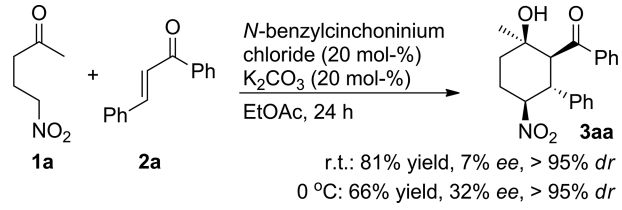
one (Table 3, entries 7, 8, and 11). (*E*)-1-(4-Nitrophenyl)-3-phenylprop-2-en-1-one (**2j**) was found to react promptly with 5-nitropentan-2-one, and the desired product (i.e., **3aj**) was formed in 49% yield (Table 3, entry 10). The yield of **3aj** could be improved to 67% when the domino reaction was carried out at 0 °C for 20 h. It was found that (*E*)-1-(4-methoxyphenyl)-3-*p*-tolylprop-2-en-1-one (**2p**) reacted with 5-nitropentan-2-one quite slowly to give the desired product (i.e., **3ap**) in 60% yield after 144 h (Table 3, entry 16). Another γ-nitro ketone was also investigated. When 6-nitrohexan-3-one (**1b**) was used to react with chalcone, six-membered-ring carbocycle **3ba** was isolated in 93% yield with >95% *dr* from the domino reaction after 8 h (Table 3, entry 18).

We also explored the reactivity of the Bu_4NI/KOH system with enones other than chalcones. The domino reaction between 5-nitropentan-2-one and (*E*)-4-phenylbut-3-en-2-one (**2r**) gave a mixture of six-membered-ring carbocycles **3ar** and **3′ar** in a total yield of 78% and a ca. 1:3 ratio, according to HPLC analysis [Scheme 3, Equation (1)]. Cyclohexenone (**2s**) reacted with 5-nitropentan-2-one to generate the Michael adduct in 64% yield, with no further annulation product formed [Scheme 3, Equation (2)]. However, increasing the loading of both the phase-transfer catalyst and the base could lead to the formation of an annulation product after a longer time.



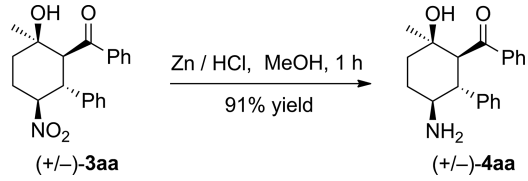
Scheme 3. Domino reactions between **1a** and other enones **2r** and **2s**.

Asymmetric phase-transfer catalysis has been used as a strategy to access complex chiral skeletons for more than thirty years. However, reports of asymmetric [4+2] cyclization under chiral phase-transfer catalysis are very rare, and racemic products were frequently obtained from [4+2] cyclization reactions with chiral phase-transfer catalysts.[16] Fully aware of the potential benefits but also of the many difficulties we would be likely to encounter, we went on to investigate the enantioselective [4+2] cyclization between 5-nitropentan-2-one (**1a**) and chalcone (**2a**). A preliminary experiment using *N*-benzylcinchoninium chloride as the chiral phase-transfer catalyst gave annulation product **3aa** in 81% yield with 7% *ee*. When the reaction was carried out at 0 °C, the *ee* of annulation product **3aa** increased to 32%, but the yield dropped to 66% (Scheme 4). Notably, the diastereoselectivities still remained at a high level.



Scheme 4. Enantioselective domino reaction between **1a** and **2a**.

Transformation of the functional groups on the functionalized six-membered-ring carbocycles was also investigated. A nitro group was reduced to an amino group with Zn/HCl in MeOH to give **4aa** as a white solid in 91% yield without optimization (Scheme 5).[17]



Scheme 5. Reduction of **3aa** to **4aa**.

Conclusions

We have developed a phase-transfer-catalyst-promoted domino reaction between γ-nitro ketones and α,β-unsaturated ketones for the construction of functionalized six-membered-ring carbocycles. Under mild reaction conditions, Bu_4NI/KOH-mediated domino reactions give the desired annulation products in good to high yields with excellent diastereoselectivities. This provides a new and efficient method for the construction of functionalized cyclohexanes. These functionalized cyclohexanes contain common functional groups such as hydroxy groups, nitro groups, carbonyl groups, and others, that could be easily transformed into other functional groups. The applications of this domino strategy for the synthesis of complex compounds are underway. These results also inspire us to continue our investigations into the enantioselective construction of functionalized six-membered-ring carbocycles. Related research with chiral organocatalysts is ongoing in our lab, and the results will be reported in the near future.

Experimental Section

General Procedure for the Domino Reaction of 5-Nitropentan-2-one with Chalcone: 5-Nitropentan-2-one **1a** (0.0787 g, 0.6 mmol) and chalcone **2a** (0.1041 g, 0.5 mmol) were dissolved in EtOAc (1.0 mL), and Bu_4NI (5 mol-%) and KOH (5 mol-%) were added to the stirred solution at room temperature. Upon completion of the reaction (monitored by TLC), the reaction mixture was purified by column chromatography on silica gel to give product **3aa** (0.1595 g, 94%). Products were fully characterized by ^1H and ^{13}C NMR spectroscopy and HRMS analysis.

Supporting Information (see footnote on the first page of this article): Characterization data; copies of the ^{1}H and ^{13}C NMR spectra for functionalized six-membered-ring carbocycles and derivative **4aa**; copies of chiral stationary phase HPLC analysis of **3aa**.

Acknowledgments

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